













ORIGINAL RESEARCH

Effects of Warfarin on the Risks of Mortality, Acute Heart Failure, and Infection Resolution in Patients With Infective Endocarditis: A Target Trial Emulation

Teddy Tai Loy Lee , MPH*; Chengsheng Ju , PhD*; Sunny Ching Long Chan , MStat; Oscar Hou In Chou, MSc; Jeffrey Shi Kai Chan , MPH; Sharen Lee , PhD; Tong Liu , PhD; Shuk Han Cheng , PhD; Yuhui Zhang , PhD; Bernard Man Yung Cheung , PhD; Abraham Ka-Chung Wai , MD; Li Wei , PhD; Gary Tse , PhD

BACKGROUND: Infective endocarditis (IE) can be complicated by acute heart failure and bacteremia, which can account for increased mortality. The role of anticoagulation with warfarin in IE is controversial. This study aimed to study the effects of anticoagulation with warfarin on survival in patients with IE, through reducing the risks of thromboembolism and possibly shortening infection time.

METHODS: This was a retrospective population-based cohort study using the Clinical Data Analysis and Reporting System from Hong Kong. Patients diagnosed with IE between January 1, 1997 and August 31, 2020 were identified using *International Classification of Diseases, Ninth Revision (ICD-9)* codes. A target pragmatic trial was emulated using the observational data with cloning-censoring-weighting approach, comparing the treatment effect of initiation warfarin within 14 days versus no warfarin on the risk of all-cause mortality, acute heart failure, and achieving negative blood culture in patients with IE. Pooled logistic regression was applied to estimate 12-week survival or cumulative incidence differences and risk ratios (RRs).

RESULTS: A total of 5121 patients with IE with an average age of 55.7 years (SD:18.9) were included. Warfarin use was associated with lower risks of all-cause mortality with 12-week survival difference of 6.5% (95% CI, 2.6%–9.9%) and RR of 0.72 (95% CI, 0.57–0.88) and a greater benefit of achieving negative blood cultures with 12-week cumulative incidence difference of 11.4% (95% CI, 5.4%–16.5%) and RR of 1.13 (95% CI, 1.06–1.20) but similar risks of acute heart failure (RR, 1.07 [95% CI, 0.87–1.30]).

CONCLUSIONS: Patients with IE initiating warfarin had significantly lower risk of mortality with potential benefits on achieving negative blood cultures, suggesting benefit in infection resolution but a similar risk of acute heart failure.

Key Words: anticoagulation ■ causal inference ■ infective endocarditis ■ trial emulation

Acute heart failure (AHF) is a common complication of infective endocarditis (IE).¹ In IE, AHF is caused by valvular regurgitation due to valvular damage by the developing vegetation, and commonly warrants cardiac surgery as treatment. In severe cases, AHF is

presented as cardiogenic shock, which presents as tissue hypoperfusion and hemodynamic instability. AHF contributes to poor prognosis in patients with IE and is a cause of the high mortality rate in patients diagnosed with IE.² Currently, international guidelines recommend

Correspondence to: Gary Tse, MD, DM, PhD, Tianjin Institute of Cardiology, The Second Hospital of Tianjin Medical University, Tianjin 300211, China. Email: gatse@hkmu.edu.hk

*T. T. L. Lee and C. Ju contributed equally.

This article was sent to Tazeen H. Jafar, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.041965>

For Sources of Funding and Disclosures, see page 9.

© 2025 The Author(s). Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Initiating warfarin within 14 days of diagnosis of infective endocarditis may lead to a significant reduction in mortality risk.
- Warfarin use may also aid infection resolution as evidenced by achievement of negative blood cultures.

What Are the Clinical Implications?

- This study supports the potential use of anticoagulation therapy in the treatment of infective endocarditis.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
IE	infective endocarditis

cardiac surgery as treatment for patients with IE presenting with severe AHF.^{3,4} However, not all patients are candidates for cardiac surgery as it is complicated by several factors, the most important of which are neurological complications. Guidelines recommend that cardiac surgery is delayed in patients suffering from intracranial hemorrhage or stroke. Cardiac surgery also poses risks of arrhythmia and formation of blood clots or introduction of new infection. As such, there are needs for treatment that potentially reduce the risks of developing AHF.

Alternatively, IE may support the persistence of bacteremia, where the vegetation acts as a stable reservoir for continuous release of bacteria to the bloodstream. This may be associated with increased mortality. Treatment of infection is thus limited to lengthy antibiotic regimens, ranging from 4 to 6 weeks of treatment, until which infection resolution is expected in patients with IE.⁵ However, the clinical utility of extended use of antibiotics is limited by the acuity of aggressive IE.

Recent studies have suggested warfarin may have a beneficial role in the management of IE.^{6,7} As AHF is induced by valvular damage originating from vegetation growth, the use of warfarin may exhibit protective effects in reducing vegetation size by preventing the recruitment of clotting factors to heart, thus slowing vegetation growth and minimizing subsequent valvular damage. Patients prescribed with warfarin have better prognosis such as decreased mortality.⁶ However, the cause of decreased mortality associated with warfarin use remains unknown. It is hypothesized that warfarin

can decrease IE mortality through a reduction in AHF events. Another mechanism would be hastening dissolution of the vegetation bacterial reservoir, leading to prompt resolution of infection. Although anticoagulation is commonly applied in the management of thromboembolism, its application remains controversial among patients with IE because of the lack of randomized controlled trials and its potential side effects.⁸ As such, current guidelines have provided few recommendations on the use of anticoagulants among patients with IE, such that there is a need for further evidence regarding the benefits of warfarin on IE.^{9,10} To the best of our knowledge, this is the first target trial emulation study evaluating the effects of warfarin initiation in a population-based cohort of adult patients with IE.

METHODS

Data Source

The data that support the findings of this study are available from the corresponding author upon reasonable request. Pseudonymized data were retrieved from the Clinical Data Analysis and Reporting System, a territory-wide electronic health care records system managed by the Hong Kong Hospital Authority, which serves an estimated 90% of the population in Hong Kong. The Clinical Data Analysis and Reporting System has previously been used extensively to conduct large population-based studies,^{11,12} including those on anticoagulation use.¹³ Informed consent was not required due to anonymity of study data.

Ethics Approval and Consent to Participate

This study was approved by The University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional Review Board (UW-20-250) and The Joint Chinese University of Hong Kong Hospital Authority New Territories East Cluster Clinical Research Ethics Committee (2019.338).

Study Design

This is a population-based cohort study applying the target trial emulation framework (ie, an observational study emulating a pragmatic clinical trial) on patients with IE using the Clinical Data Analysis and Reporting System database. The cloning-censoring-weighting approach was used to emulate a target pragmatic trial comparing the treatment effect of warfarin on all-cause mortality, AHF, and achieving negative blood cultures indicating infection resolution in patients with IE. The specification and emulation of the target trial are presented in [Table S1](#).

Eligibility Criteria

Patients aged 18 years and over with an IE diagnosis (*International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes of 424.9, 421, 93.2, 36.42) between January 1, 1997 and August 31, 2020 were eligible for this study. The baseline time (T_0) was defined as the date of the IE diagnosis during the study period. We excluded patients with previous heart failure or valvular replacement or with the use of warfarin or any other anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban, enoxaparin, fondaparinux, heparin) within 30 days before the IE diagnosis.

Treatment Strategies

We compared the treatment strategies of receiving warfarin treatment 14 days within the IE diagnosis to not starting warfarin treatment after the IE diagnosis. The 14-day (2-week) period after the IE diagnosis was used as a grace period to screen for the initiation of warfarin after IE. Indications of warfarin initiation may include prosthetic valve use, venous thromboembolism, or prevention of embolic stroke or renal infarction secondary to IE.

Follow-Up Period and Outcomes

The follow-up commenced from T_0 until an occurrence of outcome (AHF or negative blood culture), death, or 12 weeks after T_0 . The study outcomes were all-cause mortality, AHF, and negative blood culture. AHF was defined as (1) use of inotropes and vasopressors (noradrenaline, dopamine, adrenaline, phenylephrine, vasopressin, or dobutamine); (2) use of intra-aortic balloon pump (*ICD-9* procedure code 37.61); (3) use of intravenous furosemide; and (4) use of extracorporeal membrane oxygenation (*ICD-9* procedure code 39.65). The analysis on achieving negative blood culture was nested in patients who had at least 1 blood culture test after the IE diagnosis.

Covariates

Baseline covariates included age, sex, calendar year of the IE diagnosis (1997–1999, 2000–2002, 2003–2005, 2006–2008, 2009–2011, 2012–2014, 2015–2017, 2018–2020); Charlson Comorbidity Index; individual comorbidities within past 2 years before T_0 including hypertension, atrial fibrillation, diabetes, intracranial hemorrhage, chronic kidney disease, vascular disease; medications within past 30 days including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antiplatelets, beta blockers, nonsteroidal anti-inflammatory drugs; histamine-2 receptor antagonists, proton pump inhibitors, and selective serotonin reuptake inhibitors; pathogen identified from blood culture including *Staphylococci*, *Streptococci*, *Enterococci*,

and the *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* group.

We considered the role of time-varying covariates that may affect management of IE and coagulation risk during admission, which included cardiovascular surgery, heparin treatment, direct oral anticoagulant treatment, as well as all other medications that were measured at the baseline, which were updated at weekly intervals since the IE diagnosis.

All the aforementioned covariates were included in the weighting models, and the same set of covariates was applied across all 3 outcomes. A directed acyclic graph describes the causal structure between study exposure, outcomes, and confounders in Data S1.

Statistical Analysis and Emulation of the Target Trial

To emulate a target trial, we applied the cloning-censoring-weighting approach with a grace period of 14 days (2 weeks) to screen for the receipt of warfarin treatment.^{14,15} We created a data set with 2 copies of each eligible individual (ie, cloning) and assigned each of the replicates to 1 of the treatment strategies at the start of follow-up (T_0 —the IE diagnosis). Thereafter, at weekly intervals, we assessed whether replicates adhered to their assigned treatment strategy; replicates were censored if and when their actual treatment deviated from their assigned treatment strategy, thereby ensuring that replicates followed their assigned strategy. That is, if a replicate was assigned to receiving warfarin treatment, but did not receive warfarin by the end of the 14-day period, they would be censored at that point. Conversely, if a replicate is assigned to no warfarin treatment, but received warfarin at any time during the follow-up, they would be censored at that point. Any outcomes that occurred during the grace period before artificial censoring were included in both treatment arms to avoid immortal time bias. To adjust for the potential selection bias induced by this censoring, each individual received a time-varying inverse probability weight. The denominator of the weight was the probability that a replicate remained on the assigned treatment strategy conditional on baseline and time-varying characteristics. The weights created 2 pseudo-populations in which treatment was independent of measured confounding or prognostic factors. We estimated the time-varying weights by fitting logistic models for the weekly probability of remaining uncensored, including variables for time in week (in its linear and quadratic terms), and the baseline and time-varying covariates. To avoid undue influence of outliers, weights were truncated at the 99th percentile. Further details of the cloning-censoring-weighting approach are available in Data S2.

In the analysis of the AHF outcome, we considered death as the competing risk event by censoring death in a cause-specific model. Because censoring due to death may introduce selection bias, we additionally calculated an inverse probability of death weight, based on the probability of a patient being alive during each time interval, using a similar method as for the inverse probability of censoring weight. Thereby, to estimate the cause-specific risk of AHF we created a pseudo-population in which it was as if any death has not occurred.¹⁶ The final weight is the product between the inverse probability of censoring weight and death weight.

In the analysis of the negative blood culture outcome, we selected patients who had at least 1 blood culture test after the IE diagnosis. To account for the selection bias, we calculated the inverse probability weight based on the probability of having a blood culture test conditional on the baseline covariates.¹⁷ Similar to the analysis on the AHF outcome, we address the competing risk from death using an inverse probability of death weight. The final weight for the blood culture outcome was the product of inverse probability weights of blood culture test, death, and censoring due to treatment deviation.

We estimated the effect of warfarin on study outcomes using a weighted pooled logistic regression, including an indicator for treatment strategy, time in week (in its linear and quadratic terms), and their interactions to allow for nonproportional hazards. Pooled logistic regression is a discrete-time hazard model that is commonly used in the causal survival analysis.^{18,19} We used the pooled logistic regression model to estimate the probability of outcome occurrence during each follow-up time interval (weekly) under each treatment arm, and the overall cumulative survival probability from the outcome over the entire follow-up time,²⁰ which was used to plot the survival or cumulative incidence curves. To differentiate the negative end points (mortality and AHF) and positive end point (achieving negative blood culture test), we presented survival curves for the negative end points and cumulative incidence curve for the positive end point. Then, 12-week survival probability or cumulative incidence, survival or cumulative incidence differences, and risk ratios were presented accordingly with pointwise 95% CIs using a nonparametric bootstrap of 500 samples. We also approximated hazard ratios (HRs) from a Cox regression using odds ratios from the pooled logistic regression and 95% CIs with the robust variance estimator, given that the outcome is rare during each follow-up interval.²¹

Baseline characteristics were presented as median (interquartile range) for continuous variables and as numbers (%) for categorical variables. Standardized mean difference was used to evaluate the differences in baseline variables between groups. A standardized mean difference <0.2 was considered as good

balance between groups. Findings were considered to be statistically significant when the 95% CIs for risk on a relative scale did not cross 1 or when the 95% CI for risk difference on an absolute scale did not cross zero.

All analyses were performed with either R version 4.3.1 (The R Foundation) or SAS version 9.4 (SAS Institute Inc).

Sensitivity Analysis

First, we truncated the weight at 99.5th percentile rather than 99th, to evaluate the impact of extreme weights and weight truncation. Second, we changed the grace period from 2 weeks to 1 week and 3 weeks, to evaluate the impact of delayed treatment initiation. Third, we used doubly robust estimation models as the outcome models, in which the baseline covariates were adjusted in the model on top of the weights. Fourth, we used an alternative definition for AHF by excluding postoperative use of inotropes and vasopressors or any use of inotropes and vasopressors. Fifth, we stratified all analyses by calendar period of 1997 to 2008 and 2009 to 2020.

RESULTS

Patient Characteristics

A total of 5121 patients who met the eligibility criteria were included in the analysis (Figure 1). The mean age (\pm SD) of this study cohort was 55.7 years (\pm 18.9). All patients were assigned to both initiation warfarin within 14 days and no warfarin treatment strategies. Of these, 486 (9.5%) patients initiated warfarin within the 14-day grace period. After the grace period, 429 (9.1%) patients who had initiated warfarin and 4299 (90.9%) patients who had not initiated warfarin remained in the cohort (Table 1). The inverse probability weights were calculated separately for warfarin and no warfarin arms and for each study outcome, the model coefficients for the inverse probability weight for receiving warfarin treatment for each study outcome are presented in Table S2, and the distributions of the weights for each study outcome were presented in Table S3. The baseline characteristics before and after applying the inverse probability of censoring weights method after censoring over the grace period were presented in Table S4, all variables were balanced after weighting. The frequencies of time-varying covariates by treatment groups at all time points were also presented, which can be found in Table S5.

Warfarin Treatment and All-Cause Mortality

There were 424 and 1005 deaths amongst the initiating warfarin and no warfarin treatment strategy arms,

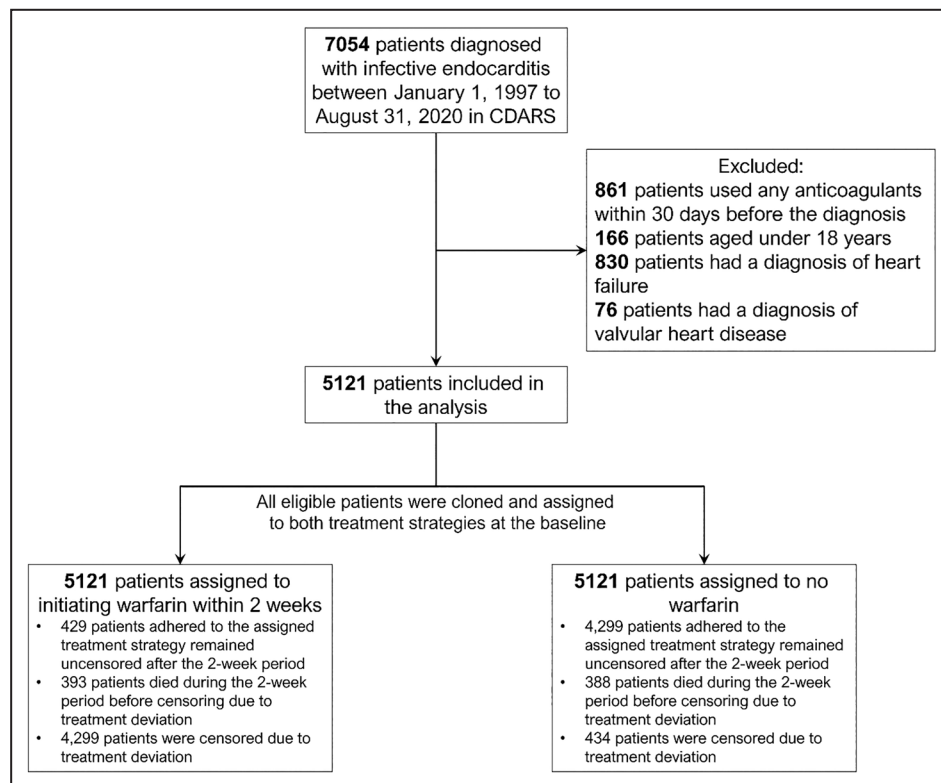


Figure 1. Selection of patients with infective endocarditis from CDARS for the trial emulation.

CDARS indicates Clinical Data Analysis and Reporting System.

respectively. The 12-week survival probability from all-cause mortality was 83.8% (95% CI, 80.7%–86.9%) for warfarin arm, and 77.3% (95% CI, 75.6%–79.0%) for no warfarin arm. The 12-week survival difference was 6.5% (95% CI, 9.9%–2.6%) and 12-week risk ratio (calculated as the ratio of 1-survival probability) was 0.72 (95% CI, 0.57–0.88) for warfarin versus no warfarin (Figure 2A). The corresponding HR, as the average risk over the follow-up period, was 0.72 (95% CI, 0.56–0.89) (Table 2).

Warfarin Treatment and AHF

There were 592 and 889 cases of AHF under the initiating warfarin and no warfarin treatment strategies, respectively. The patients with AHF were identified based on the presence of any of the 4 components: extracorporeal membrane oxygenation (n=19), intra-aortic balloon pump (n=50), use of inotropes or vasopressors (n=612), or intravenous furosemide (n=537). The 12-week survival probability from AHF was 78.0% (95% CI, 73.5%–82.2%) for the warfarin and 79.4% (95% CI, 77.8%–81.0%) for no warfarin. The 12-week survival difference was –1.4% (95% CI, –5.9% to 2.6%) and 12-week risk ratio was 1.07 (95% CI, 0.87–1.30) for warfarin versus no warfarin (Figure 2B). The corresponding HR was 1.07 (95% CI, 0.88–1.31) (Table 2).

Warfarin Treatment and Achieving Negative Blood Culture

In the analysis on negative blood culture, the 12-week absolute risk of negative blood culture was 96.4% (95% CI, 90.9%–99.9%) for the warfarin and 85.0% (95% CI, 81.9%–88.4%) for no warfarin. The 12-week difference in cumulative incidence was 11.4% (95% CI, 5.4%–16.5%) and 12-week risk ratio was 1.13 (95% CI, 1.06–1.20) for warfarin versus no warfarin (Figure 3). The corresponding HR was 1.16 (95% CI, 1.06–1.27) (Table 2). Therefore, warfarin use is associated with higher rates of recovery from bacteremia.

Sensitivity Analysis

In sensitivity analysis with varied weight truncation, grace period, doubly robust estimation, or alternative definition of AHF, the estimates were consistent with the main analysis. The 12-week risk ratio ranged from 0.71 to 0.76 for all-cause mortality, 0.87 to 1.13 for AHF, and 1.05 to 1.14 for negative blood culture (Tables S6–S10). In the stratified analysis by calendar time, warfarin was associated with a lower risk of mortality between 2009 to 2020 (HR, 0.55 [95% CI, 0.40–0.74]) but not between 1997 and 2008 (HR, 0.90 [95% CI, 0.65–1.24]), although the 95% CIs overlapped; warfarin was associated with a higher rate of negative blood culture

Table 1. Baseline Characteristics of the Study Cohorts, Before and After the Grace Period

	Baseline	After the grace period	After the grace period
	All patients (n=5121)	Warfarin (n=429)*	No warfarin (n=4299)*
Age, y (SD)	55.7 (18.9)	56.7 (16.5)	55.5 (19.2)
Male sex (%)	3420 (66.8)	252 (58.7)	2881 (67.0)
Charlson Comorbidity Index (SD)	1.6 (2.1)	1.7 (1.9)	1.6 (2.1)
Calendar y (%)			
1997–1999	827 (16.2)	2 (0.3)	751 (17.5)
2000–2002	664 (13.0)	47 (7.6)	571 (13.3)
2003–2005	596 (11.6)	54 (9.7)	505 (11.8)
2006–2008	601 (11.7)	55 (9.8)	505 (11.8)
2009–2011	588 (11.5)	64 (12.0)	470 (10.9)
2012–2014	574 (11.2)	50 (9.6)	471 (11.0)
2015–2017	657 (12.8)	79 (12.9)	532 (12.4)
2018–2020	614 (12.0)	78 (13.6)	494 (11.5)
Comorbidities (%)			
Hypertension	698 (13.6)	61 (14.2)	591 (13.8)
Atrial fibrillation	284 (5.6)	90 (20.1)	169 (3.9)
Diabetes	455 (8.9)	33 (7.7)	395 (9.2)
Intracranial hemorrhage	110 (2.2)	9 (2.1)	89 (2.1)
Chronic kidney disease	217 (4.2)	11 (2.6)	189 (4.4)
Vascular disease	31 (0.6)	2 (0.5)	25 (0.6)
Recent medications (%)			
Angiotensin-converting enzyme inhibitors	385 (7.5)	55 (12.8)	310 (7.2)
Angiotensin-II receptor blocker	110 (2.2)	17 (4.0)	89 (2.1)
Beta blockers	483 (9.4)	73 (17.0)	377 (8.8)
Antiplatelets	540 (10.5)	73 (17.0)	422 (9.8)
Nonsteroidal anti-inflammatory drugs	803 (15.7)	94 (21.9)	642 (14.9)
Histamine-2 receptor antagonists	668 (13.0)	83 (13.6)	527 (12.3)
Proton pump inhibitors	557 (10.9)	55 (12.8)	448 (10.4)
Selective serotonin receptor inhibitors	43 (0.8)	4 (0.9)	38 (0.9)
Pathogen from blood culture (%)			
Staphylococci	1025 (20.0)	42 (9.8)	824 (19.2)
Streptococci	701 (13.7)	30 (7.0)	628 (14.6)
Enterococci	101 (2.0)	7 (1.6)	87 (2.0)
<i>Haemophilus</i> species, <i>Aggregatibacter</i> species, <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , and <i>Kingella kingae</i>	35 (0.7)	0 (0)	35 (0.8)

*These numbers do not add up to the total number of patients as some patients who experienced study outcomes or administrative censoring over the grace period did not remain in the cohort after 2 weeks.

test between 1997 and 2008 (HR, 1.25 [95% CI, 1.06–1.47]) but not between 2009–2020 (HR, 1.05 [95% CI, 0.97–1.14]) because the 12-week rate of achieving negative blood culture was high in both groups (warfarin, 99.4%; no warfarin, 96.5%). No association with AHF was observed in both strata (Table S11).

DISCUSSION

This is the first target trial emulation evaluating the risk and benefits of warfarin initiation in patients with IE.

Although we found that patients with IE taking warfarin had a significantly lower risk of mortality and greater benefits on achieving negative blood cultures. However, the risk of AHF was not reduced. These findings extend our recent work using a propensity score matching approach to evaluate the treatment effects of warfarin on thromboembolic as well as hemorrhagic complications.⁶

The latest guidelines by the European Society of Cardiology for the management of endocarditis have recently been published in 2023.⁵ On the use of anticoagulation, the guidelines mentioned that patients with

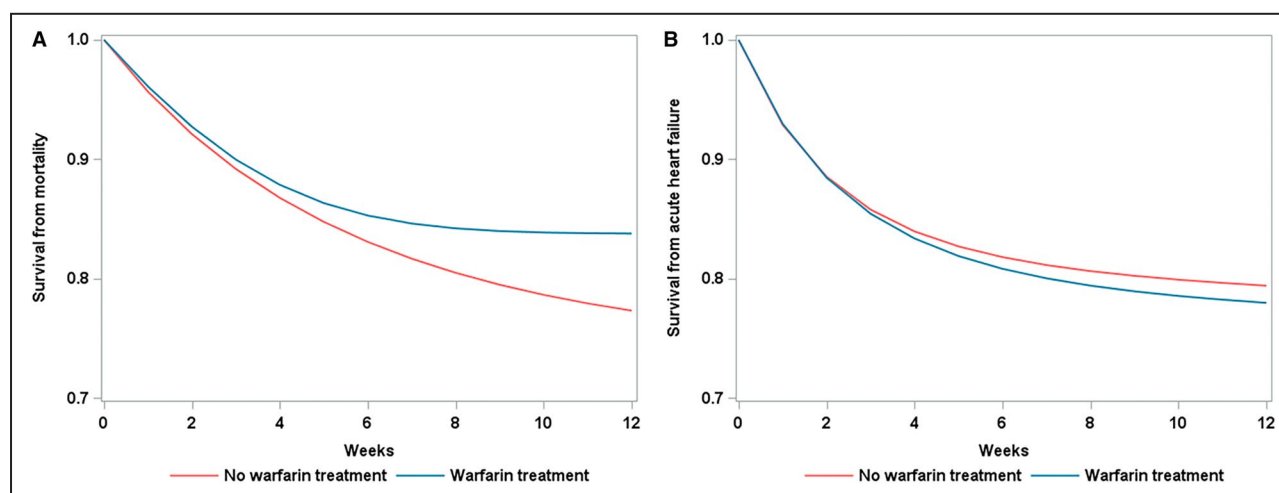


Figure 2. Weighted survival curves under warfarin versus no warfarin treatment. **A**, from all-cause mortality; **B**, from acute heart failure.

it does not appear to affect the “risk of stroke, cerebrovascular haemorrhage, or mortality at 10 weeks” in left-sided IE, and thus it was reasonable to continue anticoagulation if there is a preexisting indication in the absence of other contraindications. A recent review article has appraised the evidence for and against initiation of anticoagulation in the context of IE, published before the European Society of Cardiology guidelines were available.⁸ The recommendation was that “interruption of anticoagulation without weighty reasons should not be considered.” Another recent systematic review of observational studies in 2024 further strengthened this recommendation by showing that anticoagulation therapy may reduce the risk of in-hospital death after IE although it provided no benefits in stroke.²² The present study findings align with these previous data and provide additional evidence that anticoagulation using warfarin can be beneficial in terms of mortality by achieving negative blood cultures. Due

to the lack of planned microbiological follow-up in the current retrospective data, our analysis on achieving negative blood culture is exploratory in nature as such investigation depends on strain of pathogen, fever response, and local ward practices that varied in the real world over follow-up period. Further prospective studies are needed to further investigate the mechanism behind warfarin and the achievement of negative culture results.

The role of warfarin in the management of IE remains controversial, because warfarin use was not associated with reducing risks of stroke compared with its counterparts.^{22–24} Currently, the compelling indication for warfarin in IE included patients with mechanical heart valves, ventricular assisted device, or atrial fibrillation with mitral stenosis.^{25,26} In our previous study, in keeping with the current literatures, we found that the lowering of the mortality was not linked to lower risks of ischemic stroke events. Instead, the result hinted the

Table 2. Twelve-Week Absolute Risks, Risk Differences, Risk Ratios, and Hazard Ratios for All-Cause Mortality, AHF, and Negative Blood Culture Under Initiating Warfarin and Versus No Warfarin

Treatment	No. of patients	No. of patient-weeks	No. of outcomes	12-week absolute risk (%) (95% CI)	12-week risk difference (%) (95% CI)	12-week risk ratio (95% CI)	Hazard ratio (95% CI)
All-cause mortality							
Warfarin	5121	14 140	424	16.2 (13.1 to 19.3)	−6.5 (−9.9 to −2.6)	0.72 (0.57 to 0.88)	0.72 (0.56 to 0.89)
No warfarin	5121	46 105	1005	22.7 (21.0 to 24.4)	Reference	Reference	Reference
AHF							
Warfarin	5121	12 837	592	22.0 (17.8 to 26.5)	1.4 (−2.6 to 5.9)	1.07 (0.87 to 1.30)	1.07 (0.88 to 1.31)
No warfarin	5121	42 661	889	20.6 (19.0 to 22.2)	Reference	Reference	Reference
Negative blood culture							
Warfarin	3662	5155	2829	96.4 (90.9 to 99.9)	11.4 (5.4 to 16.5)	1.13 (1.06 to 1.20)	1.16 (1.06 to 1.27)
No warfarin	3662	8275	3201	85.0 (81.9 to 88.4)	Reference	Reference	Reference

AHF indicates acute heart failure.

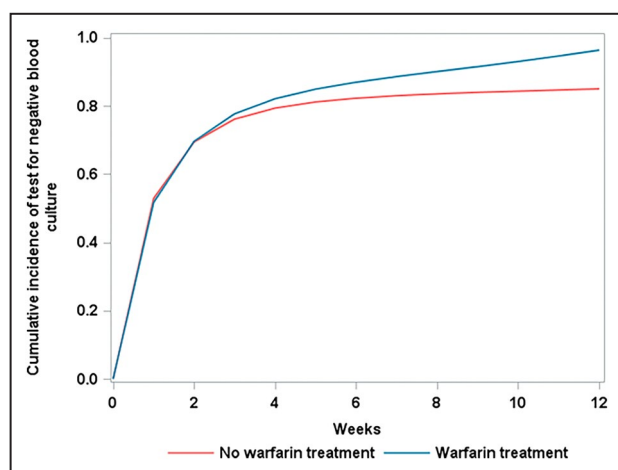


Figure 3. Weighted cumulative incidence curves under warfarin versus no warfarin treatment for test for negative blood culture.

possible role of vegetation size by anticoagulation.²⁷ In this target trial emulation study, we confirmed the mortality benefits in IE after using warfarin.

In the pathophysiology of vegetation formation in patients with IE, the initial sterile platelet-fibrin vegetation would be infected by microorganisms, which in turn, activate the coagulation pathway causing cumulation of the vegetation. Furthermore, the vegetation also provides an environment to protect the pathogen from the immune system clearance. Also, those particles may dislodge and load in the vascular beds causing thromboembolic complications including septic pulmonary embolism.²⁸

The use of warfarin may have hastened the dissolution of vegetation, thus aiding the removal of the source of bacterial infection and thus infection resolution. As such, using the anticoagulants to reduce the vegetation may be explained through the achievement of culture negativity.²⁹ This study introduces a novel approach of comparing the achievement of culture negative and AHF risks among patients with IE without warfarin. Although this study did not assess vegetation size, the shorter time to event and lower number of events for achieving a negative blood culture would support this hypothesis. Given the potential implications for infection control and hemodynamic stability, future studies should explore the role of anticoagulation in relation to septic shock and vegetation burden, ideally incorporating imaging and microbiological end points.

Partly owing to limited evidence, the role of anticoagulation in IE has been controversial. Previous observational studies on this topic investigated the role of anticoagulation in reducing possible neurological complications, with mixed results; In 1999, Tornos et al. first suggested that anticoagulant use contributed to higher mortality in prosthetic valve IE due to

intracranial hemorrhage.³⁰ Later in 2011, Syngg-Martin et al. found that patients with ongoing warfarin treatment had lower risk of cerebrovascular complications such as ischemic infarction and cerebral infection.³¹ Garcia-Cabrera et al. suggested an association between anticoagulant use and ischemic stroke or hemorrhage and recommended transitory discontinuation of anticoagulants in IE.³² In contrast, our previous study of 7054 patients with IE found no association between warfarin use and 90-day risks of intracranial hemorrhage or ischemic stroke.⁶ However, certain IE conditions may be predisposed to elevated bleeding risk, such as presence of embolic infarctions, which may further undergo hemorrhagic transformation⁸; *S. Aureus* infections are also suggested to be associated with higher bleeding risk.³³ Not all patients with IE are ideal candidates for warfarin and thus the decision to initiate anticoagulation remains individualized.

The use of antiplatelet agents in IE has similarly been controversial. It is theorized that inhibition of platelet activation prevents bacteria from attaching to damaged surfaces on the endocardium, thus reducing the risk of developing thromboembolism.³⁴ In animal studies, aspirin was demonstrated to reduce bacterial titer and inhibit vegetation growth.^{35,36} One observational study found antiplatelet use to be associated with lower 90-day mortality but did not reduce cardioembolic events.³⁷

Routinely collected, observational data have been used to estimate treatment effects in pharmacoepidemiological studies. However, even with propensity score matching or other matching methods, it is difficult to infer causality due to potential self-inflicted bias from inappropriate study designs or analyses other than confounding control. The target trial emulation framework originally proposed by Hernán and Robins provides a way to reduce bias and emulating a clinical trial as closely as possible.³⁸ This is particularly advantageous when a randomized controlled trial is not available or not feasible. In our case, randomization was emulated via cloning individuals and assigning each replicate to a treatment strategy, as the treatment is indistinctive at the baseline.³⁹ This approach effectively minimized the time-related bias without introducing selection bias. To deal with time-varying confounders and enhance exchangeability over time, we calculated time-varying inverse probability weight for each individual at each time.³⁹ Using causal analytical approaches, we have been able to produce a comprehensive analysis with both absolute and relative risks given which may help better inform the clinical practice. Furthermore, with the trial emulation approach, a Consolidated Standards of Reporting Trials-like flowchart can be constructed, as is the case in randomized controlled trials.⁴⁰ Overall, the current study has made substantial improvements in the design and

analysis of observational data in answering this question as compared with existing research.^{22,27}

This study has several limitations. First, all diagnoses were ascertained from ICD-9 codes, and individual data adjudication was not possible. Nonetheless, the Clinical Data Analysis and Reporting System has been used extensively in research with demonstrable data completeness and coding accuracy.^{41–43} Specifically, there was incomplete identification of the causative pathogen. The causal agent was identified in only approximately one third of the IE episodes, which may introduce residual confounding due to the variation in prognosis and treatment response associated with different pathogens. Future studies with more comprehensive microbial data are warranted to better elucidate the heterogeneity of treatment effect of warfarin. Second, the dosage of warfarin, as well as whether therapeutic range was achieved, was not taken into consideration. Third, significant interethnic and interracial differences exist in the antithrombotic efficacy and bleeding risks of anticoagulants,⁴⁴ meaning that our results, which are derived from mainly Han Chinese patients, may not be directly generalizable to patients of other ethnicities or races. Lastly, the causal inference from our study is based on the assumption of no unmeasured confounding, which is unverifiable in current setting. We observed that postbaseline cardiac surgeries and use of other cardiovascular medications such as antiplatelets and other anticoagulants are more common in the warfarin arm. Although we controlled for these factors using a time-varying inverse probability weighting method, residual confounding may affect our analysis as these factors are likely to affect the prognosis of IE.

CONCLUSIONS

This cohort study applying the target trial emulation framework found that warfarin use was associated with a significantly lower risk of mortality with benefits on achieving negative blood cultures but similar risk of AHF.

ARTICLE INFORMATION

Received February 23, 2025; accepted June 10, 2025.

Affiliations

Department of Emergency Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China (T.T.L., S.C.C., A-C.W.); Cardiovascular Pharmacology Unit, Cardiovascular Analytics Group, PowerHealth Research Institute, Hong Kong, China (T.T.L., O.H.C., J.S.C., S.L., G.T.); Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (C.J., L.W.); Institute of Cardiovascular Science, University College London, London, United Kingdom (C.J.); Division of Clinical Pharmacology, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China (O.H.C., B.M.C.); Tianjin Institute of Cardiology, The Second Hospital of Tianjin Medical University, Tianjin, China (T.L., G.T.); Department of Biomedical Sciences, City University of Hong Kong,

Hong Kong, China (S.H.C.); Heart Failure Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (Y.Z.); and School of Nursing and Health Sciences, Hong Kong Metropolitan University, Hong Kong, China (G.T.).

Acknowledgments

Author contributions: Teddy Tai Loy Lee, Chengsheng Ju, and Gary Tse contributed to the study conception. Teddy Tai Loy Lee, Chengsheng Ju, Li Wei, and Gary Tse designed the study. Teddy Tai Loy Lee and Gary Tse contributed to data acquisition. Teddy Tai Loy Lee and Chengsheng Ju conducted the literature review, performed the data analysis, drafted the first version of the article and contributed equally to this work. All authors contributed to interpretation of data and critically revised the article for important intellectual content. All authors approved the final version. Gary Tse is the guarantor.

Sources of Funding

This work was funded by the Tianjin Key Medical Discipline (Specialty) Construction Project (project number: TJYXZDXK-029A) a Research Impact Fund from Hong Kong Metropolitan University (Project Reference No. RIF/2022/2.2). The funders played no role in any part of this study.

Disclosures

None.

Supplemental Material

Data S1–S2
Tables S1–S11

REFERENCES

- Pericàs JM, Hernández-Meneses M, Muñoz P, Martínez-Sellés M, Álvarez-Uría A, de Alarcón A, Gutiérrez-Carretero E, Goenaga MA, Zarauza MJ, Falces C, et al. Characteristics and outcome of acute heart failure in infective endocarditis: focus on cardiogenic shock. *Clin Infect Dis*. 2021;73:765–774. doi: [10.1093/cid/ciab098](https://doi.org/10.1093/cid/ciab098)
- Mir T, Uddin M, Qureshi WT, Regmi N, Tleyjeh IM, Saydain G. Predictors of complications secondary to infective endocarditis and their associated outcomes: a large cohort study from the National Emergency Database (2016–2018). *Infect Dis Ther*. 2022;11:305–321. doi: [10.1007/s40121-021-00563-y](https://doi.org/10.1007/s40121-021-00563-y)
- Pettersson GB, Hussain ST. Current AATS guidelines on surgical treatment of infective endocarditis. *Ann Cardiothorac Surg*. 2019;8:630–644. doi: [10.21037/acs.2019.10.05](https://doi.org/10.21037/acs.2019.10.05)
- Prendergast BD, Tornos P. Surgery for infective endocarditis. *Circulation*. 2010;121:1141–1152. doi: [10.1161/CIRCULATIONAHA.108.773598](https://doi.org/10.1161/CIRCULATIONAHA.108.773598)
- Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, Caselli S, Doenst T, Ederhy S, Erba PA, et al. 2023 ESC guidelines for the management of endocarditis. *Eur Heart J*. 2023;44:3948–4042. doi: [10.1093/eurheartj/ehad193](https://doi.org/10.1093/eurheartj/ehad193)
- Lee TTL, Chan SCL, Chou OHI, Lee S, Chan JSK, Liu T, Chang C, Wong WT, Lip GYH, Cheung BMY, et al. Initiation of warfarin is associated with decreased mortality in patients with infective endocarditis: a population-based cohort study. *Thromb Res*. 2023;233:1–9.
- Preston AH, Williams S, Archer J. A review of the role of anticoagulation for patients with infective endocarditis and embolic stroke. *Clin Case Reports*. 2016;4:513–516. doi: [10.1002/ccr3.556](https://doi.org/10.1002/ccr3.556)
- Zhu X, Wang Z, Ferrari MW, Ferrari-Kuehne K, Hsi DH, Tse G, Zhou Q, Liang H, Zhang Y, Zhang J. Management of anticoagulation in patients with infective endocarditis. *Thromb Res*. 2023;229:15–25. doi: [10.1016/j.thromres.2023.06.010](https://doi.org/10.1016/j.thromres.2023.06.010)
- Habib G, Lancellotti P, Antunes MJ, Bongiorno MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, lung B, 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. doi: [10.1093/eurheartj/ehv319](https://doi.org/10.1093/eurheartj/ehv319)
- Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of

- the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e72–e227. doi: [10.1161/CIR.0000000000000923](https://doi.org/10.1161/CIR.0000000000000923)
11. Zhou J, Lee S, Wang X, Li Y, Wu WKK, Liu T, Cao Z, Zeng DD, Leung KSK, Wai AKC, et al. Development of a multivariable prediction model for severe COVID-19 disease: a population-based study from Hong Kong. *NPJ Digit Med*. 2021;4:66. doi: [10.1038/s41746-021-00433-4](https://doi.org/10.1038/s41746-021-00433-4)
 12. Lee S, Zhou J, Guo CL, Wong WT, Liu T, Wong ICK, Jeevaratnam K, Zhang Q, Tse G. Predictive scores for identifying patients with type 2 diabetes mellitus at risk of acute myocardial infarction and sudden cardiac death. *Endocrinol Diabetes Metab*. 2021;4:e00240. doi: [10.1002/edm2.240](https://doi.org/10.1002/edm2.240)
 13. Zhou J, Lee S, Liu X, Itlaf Satti D, Tai Loy Lee T, Hou In Chou O, Chang C, Roevers L, Tak Wong W, Ka Chung Wai A, et al. Hip fractures risks in edoxaban versus warfarin users: a propensity score-matched population-based cohort study with competing risk analyses. *Bone*. 2022;156:116303. doi: [10.1016/j.bone.2021.116303](https://doi.org/10.1016/j.bone.2021.116303)
 14. Maringe C, Benitez Majano S, Exarchakou A, Smith M, Rachet B, Belot A, Leyrat C. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol*. 2020;49:1719–1729. doi: [10.1093/ije/dyaa057](https://doi.org/10.1093/ije/dyaa057)
 15. Chen A, Ju C, Mackenzie IS, MacDonald TM, Struthers AD, Wei L, Man KKC. Impact of beta-blockers on mortality and cardiovascular disease outcomes in patients with obstructive sleep apnoea: a population-based cohort study in target trial emulation framework. *Lancet Regional Health Europe*. 2023;33:100715.
 16. Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernan MA. A causal framework for classical statistical estimands in failure-time settings with competing events. *Stat Med*. 2020;39:1199–1236. doi: [10.1002/sim.8471](https://doi.org/10.1002/sim.8471)
 17. Thomas DC. Estimating the effect of targeted screening strategies: an application to colonoscopy and colorectal cancer. *Epidemiology*. 2017;28:470–478. doi: [10.1097/EDE.0000000000000668](https://doi.org/10.1097/EDE.0000000000000668)
 18. Dickerman BA, Garcia-Albeniz X, Logan RW, Denaxas S, Hernan MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25:1601–1606. doi: [10.1038/s41591-019-0597-x](https://doi.org/10.1038/s41591-019-0597-x)
 19. Emilsson L, Garcia-Albeniz X, Logan RW, Caniglia EC, Kalager M, Hernan MA. Examining bias in studies of statin treatment and survival in patients with cancer. *JAMA Oncol*. 2018;4:63–70. doi: [10.1001/jamaoncol.2017.2752](https://doi.org/10.1001/jamaoncol.2017.2752)
 20. Hernan MA. The hazards of hazard ratios. *Epidemiology*. 2010;21:13–15. doi: [10.1097/EDE.0b013e3181c1ea43](https://doi.org/10.1097/EDE.0b013e3181c1ea43)
 21. Green MS, Symons MJ. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis*. 1983;36:715–723. doi: [10.1016/0021-9681\(83\)90165-0](https://doi.org/10.1016/0021-9681(83)90165-0)
 22. Caldonazo T, Musleh R, Moschovas A, Kirov H, Franz M, Haeusler KG, Faerber G, Doenst T, Günther A, Diab M. Antithrombotic therapy in patients with infective endocarditis: a systematic review and meta-analysis. *JACC Adv*. 2024;3:3. doi: [10.1016/j.jacadv.2023.100768](https://doi.org/10.1016/j.jacadv.2023.100768)
 23. 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. doi: [10.1155/2014/254187](https://doi.org/10.1155/2014/254187)
 24. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, Doco-Leconte T, Eisen DP, Fortes CQ, Fowler VG Jr, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). *Am Heart J*. 2007;154:1086–1094. doi: [10.1016/j.ahj.2007.07.023](https://doi.org/10.1016/j.ahj.2007.07.023)
 25. Chaudhry SP, DeVore AD, Vidula H, Nassif M, Mudy K, Birati EY, Gong T, Atturi P, Pham D, Sun B, et al. Left ventricular assist devices: a primer for the general cardiologist. *J Am Heart Assoc*. 2022;11:e027251. doi: [10.1161/JAHA.122.027251](https://doi.org/10.1161/JAHA.122.027251)
 26. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: [10.1093/eurheartj/ehw210](https://doi.org/10.1093/eurheartj/ehw210)
 27. Lee TTL, Chan SCL, Chou OHI, Lee S, Chan JSK, Liu T, Chang C, Wong WT, Lip GYH, Cheung BMY, et al. Initiation of warfarin is associated with decreased mortality in patients with infective endocarditis: a population-based cohort study. *Thromb Res*. 2024;233:1–9. doi: [10.1016/j.thromres.2023.11.009](https://doi.org/10.1016/j.thromres.2023.11.009)
 28. Galzerano D, Pergola V, Kinsara AJ, Vriz O, Elmahi I, Al Sergani A, Khalil F, Cittadini A, Di Giannuario G, Colonna P. Right-sided infective endocarditis and pulmonary embolism: a multicenter study. *Monaldi Arch Chest Dis*. 2022;92:2251.
 29. Werdan K, Dietz S, Löffler B, Niemann S, Bushnaq H, Silber RE, Peters G, Müller-Werdan U. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. *Nat Rev Cardiol*. 2014;11:35–50. doi: [10.1038/nrcardio.2013.174](https://doi.org/10.1038/nrcardio.2013.174)
 30. Tornos P, Almirante B, Mirabet S, Permanyer G, Pahissa A, Soler-Soler J. Infective endocarditis due to *Staphylococcus aureus*: deleterious effect of anticoagulant therapy. *Arch Intern Med*. 1999;159:473–475. doi: [10.1001/archinte.159.5.473](https://doi.org/10.1001/archinte.159.5.473)
 31. 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. doi: [10.1007/s10096-010-1063-3](https://doi.org/10.1007/s10096-010-1063-3)
 32. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, Lomas JM, Galvez-Acebal J, Hidalgo-Tenorio C, Ruiz-Morales J, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127:2272–2284. doi: [10.1161/CIRCULATIONAHA.112.000813](https://doi.org/10.1161/CIRCULATIONAHA.112.000813)
 33. Molina CA, Selim MH. Anticoagulation in patients with stroke with infective endocarditis: the sword of Damocles. *Stroke*. 2011;42:1799–1800. doi: [10.1161/STROKEAHA.111.622423](https://doi.org/10.1161/STROKEAHA.111.622423)
 34. Morelli C, Rocca B, Gigante B. Infective endocarditis and antithrombotic therapy. *Cardiology*. 2024;149:513–522. doi: [10.1159/000538549](https://doi.org/10.1159/000538549)
 35. Nicolau DP, Freeman CD, Nightingale CH, Quintiliani R, Coe CJ, Maderazo EG, Cooper BW. Reduction of bacterial titers by low-dose aspirin in experimental aortic valve endocarditis. *Infect Immun*. 1993;61:1593–1595. doi: [10.1128/iai.61.4.1593-1595.1993](https://doi.org/10.1128/iai.61.4.1593-1595.1993)
 36. Kupferwasser LI, Yeaman MR, Shapiro SM, Nast CC, Sullam PM, Filler SG, Bayer AS. 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. doi: [10.1161/01.CIR.99.21.2791](https://doi.org/10.1161/01.CIR.99.21.2791)
 37. Pepin J, Tremblay V, Bechard D, Rodier F, Walker C, Dufresne D, Lafontaine A, Li N, Lacroix C, Lanthier L. Chronic antiplatelet therapy and mortality among patients with infective endocarditis. *Clin Microbiol Infect*. 2009;15:193–199. doi: [10.1111/j.1469-0691.2008.02665.x](https://doi.org/10.1111/j.1469-0691.2008.02665.x)
 38. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758–764. doi: [10.1093/aje/kwv254](https://doi.org/10.1093/aje/kwv254)
 39. Scola G, Chis Ster A, Bean D, Pareek N, Emsley R, Landau S. Implementation of the trial emulation approach in medical research: a scoping review. *BMC Med Res Methodol*. 2023;23:186. doi: [10.1186/s12874-023-02000-9](https://doi.org/10.1186/s12874-023-02000-9)
 40. Hansford HJ, Cashin AG, Jones MD, Swanson SA, Islam N, Douglas SRG, Rizzo RRN, Devonshire JJ, Williams SA, Dahabreh IJ, et al. Reporting of observational studies explicitly aiming to emulate randomized trials: a systematic review. *JAMA Netw Open*. 2023;6:e2336023. doi: [10.1001/jamanetworkopen.2023.36023](https://doi.org/10.1001/jamanetworkopen.2023.36023)
 41. Chan JSK, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, Satti DI, Tang P, Tse G, Ng CF. Long-term cardiovascular burden in prostate cancer patients receiving androgen deprivation therapy. *Eur J Clin Invest*. 2023;53:e13932. doi: [10.1111/eci.13932](https://doi.org/10.1111/eci.13932)
 42. Chan JSK, Satti DI, Lee YHA, Hui JMH, Lee TTL, Chou OHI, Wai AKC, Ciobanu A, Liu Y, Liu T, et al. High visit-to-visit cholesterol variability predicts heart failure and adverse cardiovascular events: a population-based cohort study. *Eur J Prev Cardiol*. 2022;29:e323–e325. doi: [10.1093/eurjpc/zwac097](https://doi.org/10.1093/eurjpc/zwac097)
 43. Gao X, Zhang N, Lu L, Gao T, Hou In Chou O, Wong WT, Chang C, Wai AKC, Lip GYH, Zhang Q, et al. New-onset syncope in diabetic patients treated with sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors: a Chinese population-based cohort study. *Eur Heart J*. 2023;10:103–117. doi: [10.1093/ehjcvp/pvad086](https://doi.org/10.1093/ehjcvp/pvad086)
 44. Tamargo J, Kaski JC, Kimura T, Barton JC, Yamamoto K, Komiyama M, Drexel H, Lewis BS, Agewall S, Hasegawa K. Racial and ethnic differences in pharmacotherapy to prevent coronary artery disease and thrombotic events. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:738–751. doi: [10.1093/ehjcvp/pvac040](https://doi.org/10.1093/ehjcvp/pvac040)