The role of antiaggregant agents and anticoagulants in the prevention of aortic valve endocarditis: A double-cohort retrospective study

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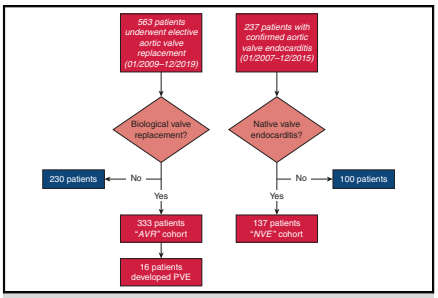
ABSTRACT

Objective: Antiaggregants (Ag) could prevent infective endocarditis (IE) in preclinical studies. In this study we investigated whether Ag or anticoagulants (Ac) were also protective in humans.

Methods: In part I we determined the incidence of IE of bioprosthetic aortic valves (PVE) in 333 consecutive patients who underwent aortic valve replacement for noninfective aortic insufficiency between 2009 and 2019. In part II we retrospectively analyzed data of 137 patients who had developed IE of the native aortic valve (NVE) between 2007 and 2015. Multivariable Fine–Gray and logistic regression models were used to investigate associations between Ag and Ac therapy and IE.

Results: Sixteen of 333 (4.8%) aortic valve replacement recipients developed PVE after a median of 3.72 years. There was no association between Ag and PVE, whereas Ac was associated with a higher IE occurrence (no association for vitamin K antagonists but significant for fondaparinux or low molecular-weight heparins; hazard ratio, 4.61; 95% CI, 1.01-21.9). In contrast, among the 137 patients in part II, vitamin K antagonists (odds ratio [OR], 7.52; 95% CI, 2.51-22.6), double antiplatelet therapy (OR, 44.3; 95% CI, 4.83-407), novel oral Ac (OR, 4.17; 95% CI, 1.15-15.1), and fondaparinux or low molecular-weight heparins (OR, 9.87; 95% CI, 1.81-53.9), but not acetylsalicylic acid, were associated with NVE.

Conclusions: Ac were associated with IE in both cohorts, whereas Ag were not associated with PVE. This might reflect differences in the studied populations, with Ag and Ac being prescribed for conditions associated with long-term IE risk in the NVE cohort. Therefore, determining the potential protective effect of Ag and Ac will necessitate further well–controlled studies. (JTCVS Open 2021;8:301-12)



Flow diagram of the 2 study cohorts.

CENTRAL MESSAGE

The observed effect of antiaggregants and anticoagulants on the risk of infectious endocarditis might depend on study design and the setting in which they are prescribed.

PERSPECTIVE

In this dual retrospective analysis, Ac were associated with the occurrence of IE in patients at risk. In contrast, Ag were not associated with IE after valve replacement, whereas they were in the retrospective native valve IE study. This might reflect differences in the populations. Therefore, determining the possible protective effect of these drugs will necessitate further well–controlled studies.

See Commentary on page 313.

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Abbreviations and Acronyms

Ac = anticoagulants
Ag = antiaggregants
ASA = acetylsalicylic acid
AVR = aortic valve replacement
DAPT = dual antiplatelet therapy
HR = hazard ratio
IE = infective endocarditis
IQR = interquartile range
IRB = institutional review board
LMWH = low molecular-weight heparins
NOAC = novel oral anticoagulants
NVE = infective endocarditis of the native aortic valve
OR = odds ratio
PVE = infective endocarditis of the bioprosthetic aortic valve
VKA = vitamin K antagonists

Infective endocarditis (IE) is a rare but potentially life-threatening disease. Its incidence has been increasing over the past decade and health care-associated pathogens such as *Staphylococcus aureus* and *Enterococcus faecalis* gained ground.[1,2] Despite earlier diagnosis and improved treatment, 30-day mortality remains high at up to 30%. To date, very few effective, long-term prophylactic strategies are at hand. The 2015 European Society of Cardiology guidelines on the management of IE advise to use antibiotic prophylaxis only in high-risk patients undergoing high-risk procedures.[3] Furthermore, this strategy cannot rule out all sources of endocarditis, because transient bacteremia most frequently occurs during day-to-day activities such as toothbrushing.[4,5] Other strategies such as vaccines against *Staphylococcus aureus* have been studied since 1910, but have gained no ground in clinical practice so far.[6]

Cardiac endothelium is naturally resistant to transient bacteremia. However, it becomes sensitive when injured or locally inflamed, leading to the exposure of the underlying extracellular matrix and subsequent activation of proinflammatory and procoagulant pathways.[2,7] Various antiaggregants (Ag) have been shown to interact with some of the surface receptors and adhesion molecules through which pathogens such as *Staphylococcus aureus* create biofilms, shielding themselves from the immune system.[8,9] As the processes of adhesion, internalization, and dissemination of pathogens can thus in theory be prevented by Ag, they have gained attention as a potential prophylactic strategy. Initial results from animal studies have indeed shown promising results for among others aspirin, ticlopidine, ticagrelor, and clopidogrel.[9-12]

It remains unclear whether antithrombotic therapies such as anticoagulants (Ac), and Ag in particular, also exert protective effects in humans. In this study, we aimed to investigate the association between the prescription of Ag and Ac and the risk of IE in 2 retrospective cohorts.

METHODS

Study Population

The institutional review board (IRB) or equivalent ethics committee of the Univeristy Hospitals Leuven approved the study protocol and publication of data (IRB approval number S63228; Nov 15, 2019). Patient written consent for the publication of the study data was waived by the IRB because of the retrospective nature of the study. The study consisted of two parts. In part I, all consecutive patients older than 16 years who underwent aortic valve replacement (AVR) with bioprosthetic valves for noninfective aortic insufficiency between January 2009 and December 2019 were identified through the local cardiac surgery database and the hospitals electronic database. Because bioprosthetic aortic valves resemble the native aortic valve more closely in physiological terms compared with mechanical valves, the latter were excluded from the analysis. The remaining patients were included in the "AVR" cohort and the development of IE of the bioprosthetic aortic valve (PVE) was investigated. In part II, all consecutive patients with confirmed IE of the aortic valve between January 2007 and December 2015 were identified through the same databases. Patients who had IE of the native aortic valve (NVE) were included in the "NVE" cohort. Patients with bioprosthetic valves were excluded from this cohort; a detailed list of reasons for exclusion is provided in Table E1.

All patients were diagnosed according to the modified Duke criteria and treated according to the European Society of Cardiology guidelines.[3] Demographic, clinical, laboratory, and follow-up data were retrieved from information available in electronic medical records, as well as hospitalizations and outpatient consultations. The minimal period of follow-up for every patient was until hospital discharge or death.

Study Design and Objectives

The primary objective of this study was to investigate whether an association exists between antithrombotic therapies and PVE or NVE. In part I, this was achieved through a retrospective time-to-event analysis with the development of PVE after AVR surgery as the event of interest. In part II, groups based according to the prescribed antithrombotic therapy were compared among patients included in the "NVE" cohort. Secondary objectives were to investigate causative pathogens, their associated time to diagnosis of IE, and their relation to antithrombotic therapy.

Antithrombotic therapies were subdivided as follows: (1) vitamin K antagonists (VKA), including acenocoumarin, phenprocoumon, and warfarin, (2) acetylsalicylic acid (ASA) and derivates, (3) dual antiplatelet therapy (DAPT) consisting of a P2Y12 receptor antagonist and ASA, (4) novel oral Ac's (NOAC) including rivaroxaban, apixaban, edoxaban, and dabigatran, (5) P2Y12-receptor antagonists, including clopidogrel, ticagrelor, prasugrel, ticlopidine, and cangrelor, (6) fondaparinux and low molecular-weight heparins (LMWH) such as enoxaparin, dalteparin, and nadroparin, and (7) no antithrombotic therapy. Some patients received 2 or more antithrombotic therapies; these are summarized in Table E2. Although these patients were included in multiple groups, the presence of combination therapy was included as a potential confounder in the

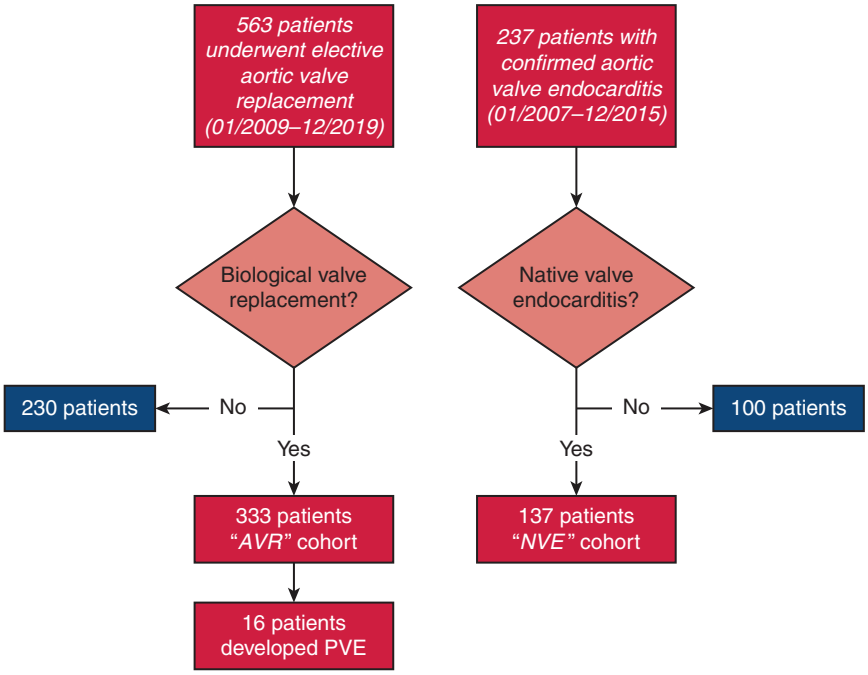

FIGURE 1. Flow diagram for the two study cohorts. *AVR*, Aortic valve replacement; *NVE*, infective endocarditis of the native aortic valve; *PVE*, infective endocarditis of the bioprosthetic aortic valve.

regression models to account for this. The initiation and duration of treatment with antithrombotic therapies in the PVE group at our center has been published prevoiusly[13]; details are given in the Appendix E1.

Statistical Analyses

Continuous variables were checked for normality using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± SD, whereas non-normally distributed variables are presented as median (interquartile range [IQR]). Categorical variables are expressed as frequency (%).

In part I, Kaplan–Meier estimates were obtained to quantify the rate of PVE over time. A multivariable Fine–Gray model was developed for each of the antithrombotic therapies, which allows for the estimation of the rate of PVE in the presence of death as a competing event. The model included the additional potential confounders such as age, sex, year of surgery, and combination therapy. Results are presented as hazard ratios (HRs) with 95% CIs. The Lagrange multiplier score test was used to estimate the effect of a therapy in case one of the groups had 0 events and a HR could therefore not be calculated.

In part II, logistic regression models were used. NVE was modeled as the binary response variable, with antithrombotic therapy as the explanatory variable. Hence, the odds of developing NVE were compared between patients who received therapy of a specific type and those who did not. Potential confounders such as age, sex, and combination therapy were included as covariates in the multivariable model. The effect of therapy on the risk of NVE is expressed as odds ratios (ORs) with 95% CIs. All analyses were performed using SAS software (version 9.4; SAS Institute Inc).

RESULTS

Study Population

Between January 2009 and December 2019, 563 patients underwent elective AVR for noninfective aortic insufficiency (Figure 1). A total of 230 mechanical aortic valves were excluded, thus leaving 333 patients with a bioprosthetic aortic valve for analysis in the "AVR" cohort. Between January 2007 and December 2015, 237 developed aortic valve endocarditis. After exclusion of cases with prosthetic valve endocarditis or other exclusion criteria (Table E1),

TABLE 1. Demographic characteristics and types of antithrombotic therapy for both cohorts

Variable	"AVR" cohort (n = 333)	"NVE" cohort (n = 137)
Number of diagnosed IE cases	16 (4.8)	137 (100)
Male sex	205 (61.6)	100 (72.9)
Age, years	74.0 (68.7-81.4)	62.1 (53.2-74.9)
Years of inclusion	2009-2019	2007-2015
Type of antithrombotic therapy		
VKA alone	49 (12.7)	16 (11.7)
ASA alone	209 (54.3)	22 (16.1)
DAPT	25 (6.5)	10 (7.3)
NOAC alone	81 (21.0)	5 (3.7)
P2Y12-receptor antagonists alone	11 (2.9)	0 (0.0)
Fondaparinux and LMWH alone	10 (2.6)	9 (6.6)
No antithrombotic therapy	0 (0.0)	75 (54.7)

Data are presented as frequency (%) or median (interquartile range), except where otherwise noted. *AVR*, Aortic valve replacement; *NVE*, infective endocarditis of the native aortic valve; *IE*, infective endocarditis; *VKA*, vitamin K antagonists; *ASA*, acetylsalicylic acid; *DAPT*, dual antiplatelet therapy; *NOAC*, novel oral anticoagulants; *LMWH*, low molecular-weight heparins.

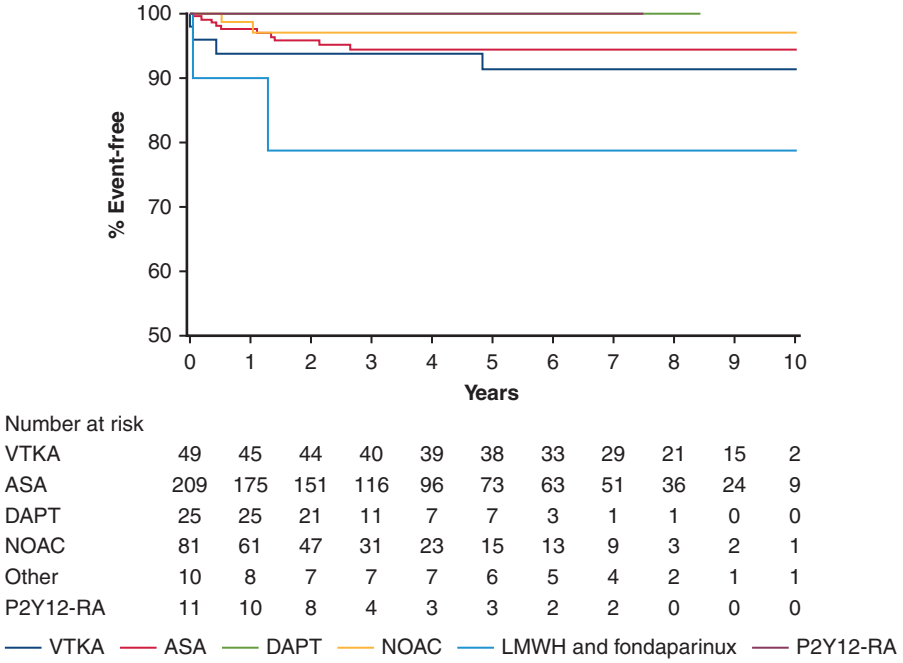

FIGURE 2. Kaplan–Meier curves representing PVE-free survival after AVR surgery, per type of antithrombotic therapy. Duration of therapy was until the last documented follow-up. Because there were no events in the P2Y12-RA and the DAPT group, both curves overlap. The 95% confidence limits for each of the curves in this figure are shown in Table E3. *VKA*, Vitamin K antagonists; *ASA*, acetylsalicylic acid; *DAPT*, dual antiplatelet therapy; *NOAC*, novel oral anticoagulant; *LMWH*, low molecular-weight heparins; *P2Y12-RA*, P2Y12-receptor antagonists.

137 patients with native aortic valve endocarditis were included in the "NVE" cohort.

Demographic characteristics and types of antithrombotic therapy are presented in Table 1. The median age was 74.0 (IQR, 68.7-81.4) years in the "AVR" cohort and 62.1 (IQR, 53.2-74.9) years in the "NVE" cohort. Participants were mainly men in both cohorts (61.6% and 72.9%, respectively). After AVR surgery, more than half of the patients (54.3%) received ASA, followed by NOAC (21.0%) and VKA (12.7%). There were no patients who did not receive antithrombotic therapy in the "AVR" cohort. In contrast, more than half of the patients in the "NVE" cohort had no antithrombotic therapy prescribed before developing IE. In the remainder of the patients in this cohort, ASA (16.1%) was most frequently used, followed by VKA (11.7%) and DAPT (7.3%). No patients in this cohort received monotherapy of P2Y12 receptor antagonists.

TABLE 2. League table representing the comparative effect of antithrombotic therapies on NVE

Index/comparison treatment	VKA alone	ASA alone	DAPT	NOAC alone	P2Y12-RA alone	Fondaparinux or LMWH alone	No antithrombotic therapy
VKA alone	1.000	5.52 (1.66-18.4)*	0.22 (0.02-2.57)	9.41 (1.26-70.4)*	†	0.43 (0.06-3.16)	7.52 (2.51-22.6)*
ASA alone	0.18 (0.05-0.60)*	1.000	0.03 (0.00-0.28)*	0.93 (0.22-4.00)	†	0.09 (0.01-0.58)	1.22 (0.61-2.48)
DAPT	4.56 (0.39-53.4)	37.9 (3.60-401)*	1.000	†	†	7.61 (0.18-318)	44.3 (4.83-407)*
NOAC alone	0.11 (0.01-0.79)*	1.08 (0.25-4.64)	†	1.000	†	0.02 (0.00-2.03)	4.17 (1.15-15.1)*
P2Y12-RA alone	†	†	†	†	1.000	†	†
Fondaparinux or LMWH alone	2.32 (0.32-17.0)	11.0 (1.73-70.1)*	0.13 (0.00-5.48)	†	†	1.000	9.87 (1.81-53.9)*
No antithrombotic therapy	0.13 (0.04-0.37)*	0.82 (0.40-1.65)	0.02 (0.00-0.21)*	0.24 (0.07-0.87)*	†	0.10 (0.02-0.55)*	1.000

The estimate (odds ratio, 95% CI) is located at the intersection of the row defining index treatment and the column defining comparison treatment. *VKA*, Vitamin K antagonists; *ASA*, acetylsalicylic acid; *DAPT*, dual antiplatelet therapy; *NOAC*, novel oral anticoagulant; *P2Y12-RA*, P2Y12-receptor antagonist; *LMWH*, low molecular-weight heparins. *$P < .05$. †The effect for comparisons could not be estimated because of low sample size.

TABLE 3. Causative pathogens in the "AVR" cohort

Pathogen	n (%)	Mean time to IE diagnosis ± SD, years
Enterococcus faecalis	5 (31.3)	0.60 ± 0.87
Streptococcus spp.	4 (25.0)	1.19 ± 1.10
Coagulase-negative *Staphylococcus*	2 (12.5)	1.19 ± 0.20
Klebsiella pneumoniae	1 (6.3)	0.05
Pseudomonas aeruginosa	1 (6.3)	1.10
Staphylococcus aureus	1 (6.3)	4.83
Negative hemoculture	2 (12.5)	0.65 ± 0.91

IE, Infective endocarditis; *SD*, standard deviation.

Part I: IE of the Bioprosthetic Aortic Valve

Of all 333 patients in the "AVR" cohort, 16 (4.8%) developed PVE after a median of 3.72 years (IQR, 1.86-7.03) after AVR. This corresponded to a risk of 0.5% per patient-year. Kaplan–Meier curves per type of antithrombotic therapy are depicted in Figure 2. Survival estimates are given in Table E3. PVE occurred in 4 patients (8.2%) receiving VKA, 10 patients (4.8%) receiving ASA, 2 patients (2.5%) receiving NOAC, and 2 patients (20.0%) receiving fondaparinux or LMWH. One of these patients was receiving VKA and ASA, and another was receiving NOAC and ASA. During follow-up, 73 patients (21.9%) died.

There was no significant association of VKA (HR, 1.79; 95% CI, 0.54-5.93; $P = .34$), ASA (HR, 0.98; 95% CI, 0.34-2.83; $P = .96$), or NOAC (HR, 0.52; 95% CI, 0.12-2.29; $P = .38$) with PVE. In contrast, a higher risk of PVE was observed with fondaparinux or LMWH (HR, 4.61; 95% CI, 1.01-21.9; $P = .05$). Because no events occurred in patients receiving DAPT or P2Y12 receptor antagonists, no HR could be calculated for these groups; however, the Lagrange multiplier score test did not reveal a significant effect for either group ($P = .24$ and $P = .45$, respectively).

Part II: NVE

Results from the logistic regression models in the "NVE" cohort are presented in a league table (Table 2). Among the 137 patients in part II, VKA (OR, 7.52; 95% CI, 2.51-22.6), DAPT (OR, 44.3; 95% CI, 4.83-407), NOAC (OR, 4.17; 95% CI, 1.15-15.1), and fondaparinux or LMWH (OR, 9.87; 95% CI, 1.81-53.9), but not ASA, were associated with increased risk for NVE compared with no antithrombotic therapy. The effect estimate for P2Y12 receptor antagonists could not be calculated because this group only included 3 patients. Furthermore, patients receiving VKA had a higher risk for NVE compared with those receiving ASA (OR, 5.52; 95% CI, 1.66-18.4) and NOAC (OR, 9.41; 95% CI, 1.26-70.4). Last, patients receiving DAPT (OR, 37.9; 95% CI, 3.60-401) and those receiving fondaparinux or LMWH (OR, 11.0; 95% CI, 1.73-70.1) had an increased risk for NVE compared with ASA.

Causative Pathogens

Among patients included in the "AVR" cohort, *E faecalis* was isolated in 5 (31.3%), *Streptococcus* species in 4 (25.0%), and coagulase-negative *Staphylococcus* in 2 (12.5%). *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were found in 1 patient each (Table 3). The mean time to PVE ranged from 0.05 years for those with *Klebsiella pneumoniae* to 4.83 years for those with *Staphylococcus aureus*.

To investigate whether certain types of antithrombotic therapy were associated with specific types of pathogens, a subgroup analysis of the 137 isolates in the "NVE" cohort was performed (Table 4). *Streptococcus* species was responsible for most cases (n = 56; 40.9%), followed by *Staphylococcus aureus* (n = 34; 24.8%), *E faecalis* (n = 20; 14.6%), and coagulase-negative *Staphylococcus* (n = 11; 8.0%). Other pathogens included *Kingella kingae* (n = 1 in the VKA group), *Propionibacterium acnes* (n = 1 in the DAPT group), *Candida albicans* (n = 1 in the LMWH group), *Escherichia coli* (n = 2 in patients with no antithrombotic therapy), *Abiotrophia defectiva* (n = 1 in patients with no antithrombotic therapy), *Aspergillus flavus* (n = 1 in patients with no antithrombotic therapy), and *Gemella haemolysans* (n = 1 in patients with no antithrombotic therapy). In 8 cases (5.8%), the culture was negative or undefined. No difference could be observed in the distribution of pathogens between therapies ($P = .43$).

TABLE 4. Causative pathogens in the "NVE" cohort

Pathogen	All (n = 137)	VKA alone (n = 16)	ASA alone (n = 22)	DAPT (n = 10)	NOAC alone (n = 5)	Fondaparinux or LMWH alone (n = 9)	No antithrombotic therapy (n = 75)
Streptococcus spp.	56 (40.9)	8 (50.0)	10 (45.5)	2 (20.0)	4 (80.0)	2 (22.2)	30 (40.0)
Staphylococcus aureus	34 (24.8)	4 (25.0)	7 (31.8)	3 (30.0)	0 (0.0)	3 (33.3)	17 (22.7)
Enterococcus faecalis	20 (14.6)	3 (18.8)	1 (4.5)	4 (40.0)	1 (20.0)	1 (11.1)	10 (13.3)
Coagulase-negative *Staphylococcus*	11 (8.0)	0 (0.0)	4 (18.2)	0 (0.0)	0 (0.0)	1 (11.1)	6 (8.0)
Other	8 (5.8)	1 (6.3)	0 (0.0)	1 (10.0)	0 (0.0)	1 (11.1)	5 (6.7)
Negative/undefined	8 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	7 (9.3)

Data are presented as n (%). *VKA*, Vitamin K antagonists; *ASA*, acetylsalicylic acid; *DAPT*, dual antiplatelet therapy; *NOAC*, novel oral anticoagulant; *LMWH*, low molecular-weight heparins.

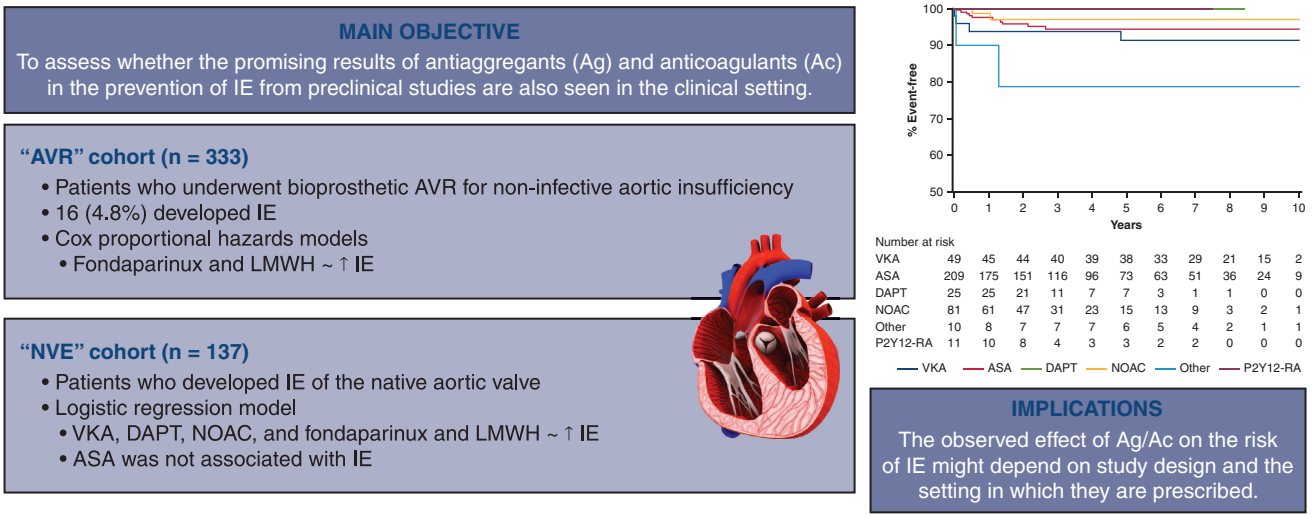

FIGURE 3. Key findings of the retrospective double-cohort study. Preclinical research has shown that antiaggregants (Ag) could prevent infective endocarditis (IE). In the present study, including 2 retrospective cohorts, we investigated whether such protective effects of these and other antithrombotic therapies are also seen in humans. In the "AVR" cohort, there was no association between Ag/anticoagulant (Ac) therapies and IE of the bioprosthetic aortic valve (PVE), although Ac tended to do less well (not statistically significant for vitamin K antagonists [*VKA*], whereas it was significant for fondaparinux or low molecular-weight heparins [*LMWH*]). In the 137 patients included in the "NVE" cohort, however, VKA, dual antiplatelet therapy (*DAPT*), novel oral anticoagulants (*NOAC*), and fondaparinux or LMWH, but not acetylsalicylic acid (*ASA*), were all associated with increased risk for NVE. This might reflect differences in the studied populations: the first being well-controlled with a progressively decreasing IE risk after AVR; the second in which Ag/Ac might have been prescribed for conditions associated with long-term IE risks, resulting in a selection bias. Therefore, determining the possible protective effect of Ag/Ac will necessitate further well-controlled studies. The 95% confidence limits for the survival curve are shown in Table E3. *AVR*, Aortic valve replacement; *P2Y12-RA*, P2Y12-receptor antagonist.

DISCUSSION

The present study, including 2 retrospective cohorts, investigated whether such protective effects of these and other antithrombotic therapies are also seen in humans (Figure 3). In part I, we found that in 333 patients who underwent AVR, there was no association between Ag/Ac therapies and PVE, although Ac tended to do less well (this was true for fondaparinux or LMWH but not for VKA). In the 137 patients included in part II, however, VKA, DAPT, NOAC, and fondaparinux or LMWH, but not ASA, were all associated with increased risk for NVE.

Nevertheless, it is worth noting that the clinical history of the 2 studied populations were quite different. In the PVE population the IE risk was rather well defined and decreased over time, in parallel to valve endothelialization (Figure 2). In the NVE study, the patients (some of them being referred to our tertiary center) were selected by the fact that they had already developed IE, without a complete knowledge of their predisposing risk factors and medical history. In addition, the risk of IE was likely to increase over time in this group. Therefore, patients of the group who received Ag or Ac could well have represented a higher risk population compared with those who did not receive Ag or Ac before infection, thus generating an untoward selection bias for IE. This underlines the potential biases that might be related to different types of analyses.

Epidemiology and Microbiology of IE

PVE is a major complication after AVR surgery, with an estimated incidence of 0.3% to 1.2% per patient-year and a cumulative risk of 5% at 10 years.[14] This corresponds to the numbers observed in the present study (0.5% per patient-year and cumulative risk of 4.8% at 9 years). With regard to timing, early PVE (≤12 months post AVR) and late PVE were found in 50% (8/16) of patients each, in agreement with data from a large Italian multicenter study.[15] Of note, all patients included in our study had received bioprosthetic valves, which tend to have a higher overall risk of IE compared with mechanical valves.[16] Furthermore, the risk of PVE gradually decreased as endothelialization occurred, resulting in late PVE having a risk similar to that of native aortic valves.[17] This might explain why most of the PVE events in our "AVR" cohort (14/16; 87.5%) occurred within the first 2 years after surgery.

From a microbiological perspective, *Streptococcus* species, *Staphylococcus aureus*, and *E faecalis* were the most common causative pathogens in IE,[18] as was confirmed by our finding that these 3 pathogens accounted for 80.3% (110/137) of all cases in the "NVE" cohort and 62.5% (10/16) in the "AVR" cohort. In PVE, the timing after AVR is known to be related to the causative pathogen. The most common microorganisms causing early PVE as

reported in the literature are *Staphylococcus aureus*, coagulase-negative *Staphylococci*, and fungi.[19] In PVE occurring later, *Enterococci* and *Streptococcus* spp predominate.[20] In our "AVR" cohort, most late PVE was indeed caused by either *E faecalis* (4/8; 50.0%) or *Streptococcus* spp (2/8; 25.0%). Interestingly, in 1 patient who developed PVE at 4.83 years after AVR surgery for calcific aortic valve disease, *Streptococcus aureus* was isolated, a pathogen which tends to be associated with early PVE. Because the patient had not undergone any procedures in the meantime, PVE likely resulted from hematogenous spread of an infection.

Antithrombotic Therapy and IE

Various preclinical studies have shown favorable results of certain types of antithrombotic therapy, and antiplatelet agents in particular, on the risk of developing IE.[9-12] After entrance into the circulation, bacteria such as *Staphylococcus aureus* can convert fibrinogen into fibrin through the expression of staphylocoagulase and von Willebrand factor–binding protein.[21] Consequently, fibrin can act as a bridge between clumping factor A on the bacterial membrane and αIIbβ3 receptor, which is found on circulating platelets.[7] This makes it possible for *Staphylococcus aureus* to not only bind to the endothelial wall of damaged valves, but also to recruit platelets for the formation of a biofilm, effectively shielding itself from the immune system.

By interacting with the αIIbβ3 receptor, ASA and P2Y12 receptor antagonists can block bacterial-induced platelet activation. In a study using a laminar flow medium, Ditkowski and colleagues[22] reported that bacterial adhesion to tissue valve or conduit heterografts was reduced by approximately 50% when either ASA or ticagrelor were used and 70% when both were combined in DAPT. Moreover, some of these agents have an additional antimicrobial action, as shown by Lancellotti and colleagues[9] in the context of ticagrelor therapy. In time-kill assays, they showed that ticagrelor exerted bactericidal activity against gram-positive strains, including *E faecalis* and methicillin-resistant *Staphylococcus aureus*. They also showed that ticagrelor inhibited biofilm growth on *Staphylococcus aureus*–preinfected implants. Furthermore, Veloso and colleagues[8,10] reported that the combination of ASA and ticlopidine, as well as abciximab, protected against *Streptococcus gordonii*, *Streptococcus gallolyticus*, *Staphylococcus aureus*, and *E faecalis* IE in an experimental rat model of prolonged low-grade bacteremia. Interestingly, in one of the studies,[8] dabigatran, an anticoagulant, also protected against IE due to *Staphylococcus aureus* but not *Streptococcus gordonii*. Supporting the latter finding, Lerche and colleagues[23] reported that dabigatran significantly reduced valve vegetation size, bacterial load, and expression of inflammatory markers when administered in combination with gentamicin in a rat model of severe aortic valve *Staphylococcus aureus* IE.

As highlighted previously, evidence from preclinical studies thus mainly exists for antiplatelet agents, although limited evidence is also available supporting efficacy of the anticoagulant dabigatran in the prevention of IE. Dabigatran reversibly binds to thrombin as well as staphylothrombin, inhibiting the conversion of fibrinogen to fibrin and enhancing fibrinolysis. Although it thus inhibits *Staphylococcus aureus*–induced platelet aggregation, it does not interfere with the activity of the bacteria.[8,21] However, experimental animal studies have consistently shown no effect of VKA on IE.[8] Of note, most preclinical research efforts have focused on *Staphylococcus aureus*, which is the main cause of early PVE but becomes relatively less important in late PVE.

Strikingly, the present study could not confirm the efficacy of any antithrombotic therapy to prevent IE in an actual clinical setting. In part I, all patients received some kind of Ag or Ac, and thus the drugs were to be compared with each other. In contrast, in part II, the prescription of these drugs was associated with an increased risk of IE compared with patients who received no treatment. The question arises as to why such association was observed and whether these results should discourage further investigation of antithrombotic therapies as a potential preventive strategy for IE. Most likely, the main reason is to be found in the fact that antithrombotic therapies are frequently prescribed for patients with concurrent cardiovascular diseases that are considered "high risk" to develop IE according to the 2017 update of the 2014 American Heart Association/American College of Cardiology guideline for the management of patients with valvular heart disease.[24] Patients who are receiving antithrombotic therapies can thus be assumed to carry a higher baseline risk of developing IE. In addition, Strom and colleagues[25] showed earlier that preexisting valve lesions as well as other conditions such as kidney diseases, diabetes, and intravenous access were all strongly associated with community-acquired IE. Interestingly, ASA, which is a drug that is widely prescribed for various cardiovascular conditions and thus not necessarily associated with "high risk" comorbidities, was not associated with IE in our study.

Although sample size restrictions and limited availability of data on comorbidities did not allow us to check this hypothesis, the prescription of antithrombotic therapies in a clinical setting might therefore primarily reflect the risk profile of these patients, rather than providing actual protection against IE. The results of this study should thus not lead to the conclusion that antithrombotic therapies have failed as a strategy to prevent IE. Some antiplatelet agents or Ac might in fact reveal favorable effects in future human trials. In any case, the current finding that none of the

antithrombotic therapies used could reduce the risk of IE until levels similar to patients not taking any of these drugs, should at least temper expectations and suggests that effects might be less pronounced than those reported in vitro studies. Well–designed randomized controlled trials and large prospective registry studies might help to provide more conclusive answers. Examples are provided by post hoc analyses of the PLATelet inhibition and patient Outcomes (PLATO) trial (NCT00391872).[9,26] Although dedicated research platforms to study the effect of Ag and Ac on the prevention of IE have not been established to date, the results of the current study critically highlight the importance of these.

Limitations

Because this was a retrospective study on results of a single tertiary care hospital, only a small sample size was available for some subgroup analyses and some comparisons could not be calculated. For example, no events occurred in patients who received DAPT or P2Y12 receptor antagonists in the "AVR" cohort and no patients who received P2Y12 receptor antagonists were included in the "PVE" cohort, limiting our ability to draw conclusions on these therapies. Furthermore, although age, sex, year of surgery, and combination therapy were included as covariates in the multivariable model, it cannot be excluded that other factors might have influenced the results. Because several of our IE patients were referred cases, we did not have full access to information on comorbidities for all of them.

CONCLUSIONS

This dual analysis of the potential of Ag and Ac therapy to prevent IE highlights the limits of comparing different types of approaches and the untoward biases related to post hoc evaluation. In part I, the cohort and questions were well defined, and the observational follow-up straightforward. However, comparing multiple drug regimens a posteriori might have resulted in statistical underpowering, which could have been solved by determining sample size in a prospective protocol. In part 2, the unavoidable limits of retrospective review of patient files became evident. In addition, the fact that this dual analysis was made in a single investigational center further emphasizes the risk of conclusion biases or misinterpretation when comparing literature data generated by unrelated research groups. Therefore, determining the possible protective effect of Ag and Ac will necessitate further well–controlled studies.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: anticoagulants, aortic valve, bioprosthetic valves, infective endocarditis, platelet aggregation inhibitors

APPENDIX E1. METHODS

Antithrombotic Management After Bioprosthetic Aortic Valve Replacement

Anticoagulation was initiated when bleeding risk was minimized and all drains were removed. Bridging with low molecular-weight heparins was started when platelet count was > 70,000/μL and/or international normalized ratio < 2. The choice for a certain type of anticoagulant and the duration of therapy was made on the basis of patient comorbidities and risk profile.[E1] The minimal duration of therapy was 3 months because the rate of thromboembolism is significantly elevated during this initial period.[E2] Aspirin was continued ad vitam.

E-References

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TABLE E1. Overview of patients excluded from part 2 of the study (N = 100)

Reason for exclusion	Patients excluded, n (%)
Prosthetic aortic valve endocarditis	71 (71.0)
Concomitant prosthetic aortic valve and mitral valve (biological or prosthetic unknown) endocarditis	25 (25.0)
Concomitant prosthetic aortic valve, mitral valve (biological or prosthetic unknown) endocarditis and tricuspid valve (biological or prosthetic unknown) endocarditis	2 (2.00)
Concomitant prosthetic aortic valve, mitral valve (biological or prosthetic unknown) endocarditis and pulmonary valve (biological or prosthetic unknown) endocarditis	1 (1.00)
Concomitant prosthetic aortic valve and tricuspid valve (biological or prosthetic unknown) endocarditis	1 (1.00)
Total patients excluded	100 (100)

TABLE E2. Overview of concomitant use of antiaggregant and anticoagulant medication by patients in both cohorts

Concomitant use of medication	Patients "AVR" cohort (n = 333)	Patients "NVE" cohort (n = 137)
Aspirin and VKA	14 (4.20%)	0 (0.0%)
Aspirin and NOAC	29 (8.71%)	0 (0.0%)
DAPT and VKA	1 (0.30%)	1 (0.73%)
NOAC and VKA	4 (1.20%)	0 (0.0%)
NOAC and P2Y12 inhibitor	7 (2.10%)	0 (0.0%)
P2Y12 inhibitor and VKA	1 (0.30%)	0 (0.0%)

Data are presented as n (%). *AVR*, Aortic valve replacement; *NVE*, infective endocarditis of the native aortic valve; *VKA*, vitamin K antagonists; *NOAC*, novel oral anticoagulant; *DAPT*, dual antiplatelet therapy.

TABLE E3. PVE-free survival following AVR surgery, per type of antithrombotic therapy: survival estimates (with 95% confidence limits) at 1 through 10 years

Group	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years	9 Years	10 Years
VKA alone	93.83 (82.08, 97.97)	93.83 (82.08, 97.97)	93.83 (82.08, 97.97)	91.43 (78.67, 96.71)	91.43 (78.67, 96.71)	91.43 (78.67, 96.71)	91.43 (78.67, 96.71)	91.43 (78.67, 96.71)	91.43 (78.67, 96.71)	93.83 (82.08, 97.97)
ASA alone	97.58 (94.27, 98.98)	95.87 (91.88, 97.92)	94.42 (89.77, 96.99)	94.42 (89.77, 96.99)	94.42 (89.77, 96.99)	94.42 (89.77, 96.99)	94.42 (89.77, 96.99)	94.42 (89.77, 96.99)	94.42 (89.77, 96.99)	97.58 (94.27, 98.98)
NOAC	98.65 (90.79, 99.81)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	97.03 (88.58, 99.25)	98.65 (90.79, 99.81)
Fondaparinux or LMWH alone	90.00 (47.30, 98.53)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	78.75 (38.09, 94.26)	90.00 (47.30, 98.53)

Duration of therapy was until the last documented follow-up. Because there were no events in the P2Y12-RA and the DAPT group, estimates could not be calculated for these therapies. *VKA*, Vitamin K antagonists; *ASA*, acetylsalicylic acid; *NOAC*, novel oral anticoagulant; *LMWH*, low molecular-weight heparins.