AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Impact of Clopidogrel on Clinical Outcomes in Patients with *Staphylococcus aureus* Bacteremia: a National Retrospective Cohort Study

Aisling R. Caffrey,[a,b,c,d] Haley J. Appaneal,[a,b,c] Kerry L. LaPlante,[a,b,c,e] Vrishali V. Lopes,[a] Erlinda R. Ulloa,[f,g] Victor Nizet,[h] George Sakoulas[h]

[a]Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, Rhode Island, USA
[b]Center of Innovation in Long-Term Support Services, Providence Veterans Affairs Medical Center, Providence, Rhode Island, USA
[c]College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, USA
[d]Warren Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, Rhode Island, USA
[e]School of Public Health, Brown University, Providence, Rhode Island, USA
[f]Department of Pediatrics, University of California, Irvine School of Medicine, Irvine, California, USA
[g]Division of Infectious Disease, Children's Hospital of Orange County, Orange, California, USA
[h]University of California, San Diego School of Medicine, La Jolla, California, USA

ABSTRACT Activated platelets have known antimicrobial activity against *Staphylococcus aureus*. Accelerated clearance of platelets induced by *S. aureus* can result in thrombocytopenia and increased mortality in patients. Recent studies suggest that P2Y12 inhibition protects platelets from accelerated clearance. We therefore evaluated the effect of P2Y12 inhibition on clinical outcomes in patients with *S. aureus* bacteremia across a large national cohort. Our retrospective cohort (2010 to 2018) included patients admitted to Veterans Affairs (VA) hospitals with blood cultures positive for *S. aureus* and treated with standard-of-care antibiotics. Employing propensity score-matched Cox proportional hazards regression models, we compared clinical outcomes in patients treated with clopidogrel for at least the 30 days prior to admission and continuing for at least 5 days after admission to patients without any P2Y12 inhibitor use in the year preceding admission. Mortality was significantly lower among clopidogrel users than P2Y12 inhibitor nonusers (n = 147 propensity score-matched pairs): the inpatient mortality hazard ratio (HR) was 0.11 (95% confidence interval [CI], 0.01 to 0.86), and 30-day mortality HR was 0.43 (95% CI, 0.19 to 0.98). There were no differences in 30-day readmission, 30-day *S. aureus* reinfection, microbiological clearance, or thrombocytopenia. Clopidogrel use at the time of infection reduced in-hospital mortality by 89% and 30-day mortality by 57% among a cohort of patients with *S. aureus* bacteremia. These results support the need to further study the use of P2Y12 inhibitors as adjunctive therapy in *S. aureus* bloodstream infections.

KEYWORDS clopidogrel, P2Y12 blockade, *Staphylococcus aureus*, bacteremia, thrombocytopenia, platelets

Despite appropriate and timely antimicrobial therapy, *Staphylococcus aureus* bloodstream infections often result in considerable morbidity and mortality across all age groups (1, 2). *S. aureus* strains are heterogeneous in their interaction with the host via their broad repertoire of virulence factors. Targeting *S. aureus* virulence factors with adjunctive therapies may improve the clinical outcomes of patients with serious *S. aureus* infections (3). Recent evidence suggests that platelet ADP P2Y12 inhibitors, such as clopidogrel, ticagrelor, and prasugrel, may be repurposed as adjunctive therapy to improve outcomes in patients with *S. aureus* bacteremia (4, 5).

Ticagrelor is an antithrombotic agent used to prevent cardiovascular events in patients

Address correspondence to Aisling R. Caffrey, Aisling_Caffrey@uri.edu.

The authors declare a conflict of interest. Aisling R. Caffrey has received research funding from AbbVie, Gilead, Merck, Pfizer, and Shionogi and has received speaking honoraria from Merck. Kerry L. LaPlante has received research funding from AbbVie, Gilead, Merck, Pfizer, and Shionogi. George Sakoulas has received consulting and speaking honoraria from Abbvie and Paratek.

Received 2 November 2021
Returned for modification 27 November 2021
Accepted 9 March 2022

with acute coronary syndrome or a history of myocardial infarction, such as in patients receiving percutaneous coronary intervention (PCI) (5). Recent evidence suggests that ticagrelor may block *S. aureus* alpha-toxin-mediated platelet cytotoxicity and induced thrombocytopenia, thereby facilitating *S. aureus* bacteremia clearance by endogenous platelet-derived antimicrobial peptides and other staphylocidal platelet activities (4, 5). Further, ticagrelor prevents platelet desialylation driven by *S. aureus* alpha-toxin (5). Desialylated platelets result in enhanced platelet clearance via the hepatic Ashwell-Morell receptor (6). As platelets are a key component of innate immunity in endovascular infections, thrombocytopenia could worsen clinical outcomes in such settings. Indeed, thrombocytopenia is a strong predictor of mortality in *S. aureus* bacteremia (7, 8).

In the context of potential benefits of P2Y12 inhibition in *S. aureus* infection, we retrospectively compared clinical outcomes of patients with *S. aureus* bacteremia already on clopidogrel at the time of infection to those of patients not on P2Y12 inhibitors. We selected clopidogrel as the exposure of interest because it was the predominant P2Y12 inhibitor (>96%) utilized among the cohort of patients with *S. aureus* bacteremia in the Veterans Affairs (VA) health care system during our study period.

(This work was presented, in part, at IDWeek 2020.)

RESULTS

Our VA-based study included 355 clopidogrel users and 11,144 nonusers, all with *S. aureus* bacteremia, with mean respective ages of 69 (standard deviation [SD], 10) and 66 (SD, 13) years and comprised of >97% males. Demographics and patient characteristics for the overall cohort and the propensity score-matched cohort are presented in Table 1. All variables included in the propensity score can be found in the footnote of Table 2 and Table S1 in the supplemental material. Propensity scores of the clopidogrel users and nonusers demonstrated complete overlap (Fig. S1, common support of the propensity score). Patient characteristics were well balanced in the propensity score-matched cohort (147 matched pairs). Absolute standardized differences before and after matching can be found in Table S1.

Platelet counts. There were no differences in mean platelet counts between clopidogrel users and P2Y12 inhibitor nonusers at the time of hospital admission in both the overall and propensity score-matched cohorts. The median platelet counts were similar in clopidogrel users (206,000/μL; interquartile range [IQR], 149,000 to 283,000) and P2Y12 inhibitor nonusers (212,000/μL; IQR, 146,000 to 296,000; $P = 0.42$) in the overall cohort. Figure 1 displays the similar mean daily platelet counts during admission for clopidogrel users and P2Y12 inhibitor nonusers in the overall and propensity score-matched cohorts. Clopidogrel users and P2Y12 inhibitor nonusers both demonstrated a nadir in the first 48 h after hospitalization, followed by a steady rise peaking at 10 to 14 days and mild decline hitting a plateau at 3 weeks and beyond in both the overall and propensity score-matched cohorts.

Clinical outcomes. Table 2 presents clinical outcomes in clopidogrel users compared with P2Y12 inhibitor nonusers. The inpatient mortality rate was 7.8% in the study population ($n = 893/11,499$). Among the propensity score-matched cohort, mortality was significantly lower among clopidogrel users: the inpatient mortality hazard ratio (HR) was 0.11 (95% confidence interval [CI], 0.01 to 0.86), and the 30-day mortality HR was 0.43 (95% CI, 0.19 to 0.98). Kaplan-Meier survival curves of inpatient mortality and 30-day mortality in the propensity score matched cohort are presented in Fig. 2 and 3. There were no other significant differences in clinical outcomes, including microbiological clearance (HR, 0.87 [95% CI, 0.62 to 1.21]) or thrombocytopenia (HR, 0.90 [95% CI, 0.57 to 1.40]) during the admission or readmission (HR, 0.93 [95% CI, 0.54 to 1.60]). The median length of bacteremia among patients with follow-up cultures was 2 days in both groups.

Clinical outcomes were assessed by baseline platelet counts, stratified by <100,000/μL and ≥100,000/μL. The number of patients with moderate thrombocytopenia (platelet count < 100,000/μL) represented only 10.0% ($n = 1,153$) of clopidogrel users and P2Y12 inhibitor nonusers. In the stratified analyses by baseline platelet count and methicillin-susceptible/methicillin-resistant *S. aureus* (MSSA/MRSA), no statistically significant

TABLE 1 Baseline demographics and patient characteristics among clopidogrel users compared with P2Y12 inhibitor nonusers in the overall and propensity score matched cohorts[a]

Patient characteristic	Value for: Overall clopidogrel users (*n* = 355)	Value for: Overall P2Y12 inhibitor nonusers (*n* = 11,144)	*P* value	Value for: Matched clopidogrel users (*n* = 147)	Value for: Matched P2Y12 inhibitor nonusers (*n* = 147)	*P* value
Age (yrs), mean (SD)*	69 (10)	66 (13)	<0.0001	70.3 (11.0)	68.3 (11.3)	0.14
Male*	352 (99.2)	10,861 (97.5)	0.04	146 (99.3)	145 (98.6)	1.0
White*	268 (75.5)	7,871 (70.6)	0.05	109 (74.2)	115 (78.2)	0.41
Hispanic or Latino, no.*	24 (6.8)	848 (7.6)	0.55	11 (7.5)	14 (9.5)	0.53
Married, no.*	158 (44.5)	4,340 (38.9)	0.03	66 (44.9)	64 (43.5)	0.81
Yr of admission*						
2010–2012	102 (28.7)	4,148 (37.2)	0.003	47 (32.0)	42 (28.6)	0.79
2013–2015	121 (34.1)	3,526 (31.6)		43 (29.3)	47 (32.0)	
2016–2018	132 (37.2)	3,470 (31.1)		57 (38.8)	58 (39.5)	
Methicillin-resistant *Staphylococcus aureus* strain*	120 (33.8)	3,886 (34.9)	0.68	51 (34.7)	52 (35.4)	0.90
Concomitant *S. aureus* in other culture sites[d]	142 (40.0)	4,715 (42.3)	0.39	50 (34.0)	58 (39.5)	0.33
Skin and soft tissue*	87 (24.5)	1,910 (17.1)	0.0003	24 (16.3)	32 (21.8)	0.23
Urine*	29 (8.2)	1,504 (13.5)	0.004	17 (11.6)	7 (4.8)	0.03
Respiratory	11 (3.1)	559 (5.0)	0.10	<5 (<3.4)	8 (5.4)	0.24
Bone joint*	11 (3.1)	590 (5.3)	0.07	7 (4.8)	7 (4.8)	1.0
Other	17 (4.8)	775 (6.9)	0.11	<5 (<3.4)	6 (4.1)	0.28
Concomitant organism in blood*	77 (21.7)	2,495 (22.4)	0.75	25 (17.0)	29 (19.7)	0.55
*Escherichia coli**	7 (2.0)	464 (4.2)	0.04	<5 (<3.4)	<5 (<3.4)	1.0
Source of admission*						
Community	167 (47.0)	5,113 (45.9)	0.66	72 (49.0)	65 (44.2)	0.41
Hospital	2 (0.6)	67 (0.6)	1.0	<5 (<3.4)	<5 (<3.4)	0.49
Nursing home	15 (4.2)	641 (5.8)	0.2	6 (4.1)	6 (4.1)	1.0
Intensive care treatment*	127 (35.8)	4,031 (36.2)	0.87	50 (34.0)	59 (40.1)	0.28
Surgery during admission*	91 (25.6)	3,043 (27.3)	0.48	35 (23.8)	31 (21.1)	0.57
Surgery 30 days prior to admission*	22 (6.2)	724 (6.5)	0.82	8 (5.4)	9 (6.1)	0.80
Health care exposures, past 90 days						
Hospitalization	174 (49.0)	4,231 (38.0)	<0.0001	59 (40.1)	58 (39.5)	0.91
Nursing home	22 (6.2)	479 (4.3)	0.08	<5 (<3.4)	5 (3.4)	0.45
Intensive care	68 (19.2)	1,003 (9.0)	<0.0001	21 (14.3)	19 (12.9)	0.73
Baseline platelet count, median (IQR)*	206 (149–283)	212 (146–296)	0.42	211 (149–289)	202 (146–260)	0.46
Body mass index, mean (SD)*	29 (7)	28 (7)	0.41	29 (7)	29 (7)	0.35
Medical conditions during admission						
Acute renal failure*	131 (31.8)	4,027 (36.1)	0.77	50 (34.0)	65 (44.2)	0.07
Endocarditis	28 (8.7)	964 (9.4)	0.69	14 (9.5)	11 (7.5)	0.53
Fever*	5 (1.4)	247 (2.2)	0.31	<5 (<3.4)	<5 (<3.4)	1.0
Pneumonia*	41 (11.6)	2,019 (18.1)	0.002	22 (15.0)	24 (16.3)	0.75
Respiratory failure*	46 (13.0)	1,623 (14.6)	0.40	18 (12.2)	26 (17.7)	0.19
Septicemia*	248 (69.9)	8,010 (71.9)	0.41	101 (68.7)	112 (76.2)	0.15
Shock*	26 (7.3)	1,021 (9.2)	0.24	10 (6.8)	15 (10.2)	0.29
P2Y12 inhibitor						
Contraindication*[b]	221 (62.3)	4,418 (39.6)	<0.0001	77 (52.4)	71 (48.3)	0.48
Indication*[c]	311 (87.6)	4,644 (41.7)	<0.0001	111 (75.5)	107 (72.8)	0.59
Medical history, previous yr						
Acute cerebrovascular disease*	75 (21.1)	810 (7.3)	<0.0001	33 (22.5)	28 (19.1)	0.47
Acute myocardial infarction*	76 (21.4)	257 (2.3)	<0.0001	9 (6.1)	15 (10.2)	0.20
Acute renal failure*	113 (31.8)	2,802 (25.1)	0.004	33 (22.5)	42 (28.6)	0.23
Alcohol abuse*	26 (7.3)	1,806 (16.2)	<0.0001	9 (6.1)	6 (4.1)	0.43
Asthma*	21 (5.9)	475 (4.3)	0.13	9 (6.1)	8 (5.4)	0.80
Atherosclerosis*	271 (76.3)	2,700 (24.2)	<0.0001	87 (59.2)	86 (58.5)	0.91
Bacterial infection*	94 (26.5)	2,298 (20.6)	0.007	34 (23.1)	29 (19.7)	0.48
Cancer/malignancy	125 (35.2)	4,118 (37.0)	0.50	60 (40.8)	55 (37.4)	0.55

(Continued on next page)

TABLE 1 (Continued)

Patient characteristic	Value for: Overall clopidogrel users (*n* = 355)	Overall P2Y12 inhibitor nonusers (*n* = 11,144)	*P* value	Value for: Matched clopidogrel users (*n* = 147)	Matched P2Y12 inhibitor nonusers (*n* = 147)	*P* value
Chronic obstructive pulmonary disease	129 (36.3)	2,787 (25.0)	<0.0001	45 (30.6)	52 (35.4)	0.39
Coagulation and hemorrhagic disorder*	28 (7.9)	1,176 (10.6)	0.11	14 (9.5)	14 (9.5)	1.0
Congestive heart failure*	158 (44.5)	2,183 (19.6)	<0.0001	48 (32.7)	52 (35.4)	0.62
Diabetes*	273 (76.9)	5,968 (53.6)	<0.0001	103 (70.1)	102 (69.4)	0.90
Infective arthritis/ osteomyelitis*	67 (18.9)	1,392 (12.5)	0.0004	22 (15.0)	19 (12.9)	0.61
Liver disease	43 (12.1)	1,672 (15.0)	0.13	17 (11.6)	14 (9.5)	0.57
Hypertension*	323 (91.0)	7,888 (70.8)	<0.0001	129 (87.8)	129 (87.8)	1.0
Peripheral visceral atherosclerosis*	163 (45.9)	1,787 (16.0)	<0.0001	48 (32.7)	32 (21.8)	0.04
Pneumonia	64 (18.0)	1,619 (14.5)	0.07	24 (16.3)	20 (13.6)	0.51
Respiratory failure*	40 (11.3)	997 (9.0)	0.13	11 (7.5)	15 (10.2)	0.41
Septicemia	54 (15.2)	1,696 (15.2)	0.99	21 (14.3)	26 (17.7)	0.43
Shock*	7 (2.0)	264 (2.4)	0.63	<5 (<3.4)	<5 (<3.4)	1.0
Skin and soft tissue infection*	113 (31.8)	3,131 (28.1)	0.12	44 (29.9)	45 (30.6)	0.90
Elixhauser, median (IQR)*	6 (4–8)	5 (3–7)	<0.0001	5 (3–7)	5 (4–7)	0.67
Infections, previous yr	158 (44.5)	4,144 (37.2)	0.005	56 (38.1)	56 (38.1)	1.0
*Staphylococcus aureus**	101 (28.5)	2,369 (21.3)	0.001	34 (23.1)	35 (23.8)	0.89
Medications, previous yr						
Aspirin	109 (30.7)	1,599 (14.4)	<0.0001	31 (21.1)	33 (22.5)	0.78
Statin	167 (47.0)	2,258 (20.3)	<0.0001	52 (35.4)	59 (40.1)	0.40
Oseltamivir	<5 (<1.4)	39 (0.4)	0.04	<5 (<3.4)	<5 (<3.4)	1.0
Medications during admission						
Aspirin*	253 (71.3)	4,481 (40.2)	<0.0001	85 (57.8)	90 (61.2)	0.55
Statin*	307 (86.5)	4,713 (42.3)	<0.0001	114 (77.6)	114 (77.6)	1.0
Oseltamivir*	9 (2.5)	178 (1.6)	0.17	<5 (<3.4)	9 (6.1)	0.003
Antibiotic use, previous 30 days	112 (31.6)	3,060 (27.5)	0.09	42 (28.6)	34 (23.1)	0.29
Antibiotics during admission						
Ampicillin-sulbactam*	27 (7.6)	610 (5.5)	0.08	13 (8.8)	8 (5.4)	0.26
Carbapenem	34 (9.6)	1,264 (11.3)	0.30	11 (7.5)	12 (8.2)	0.83
Ceftaroline	10 (2.8)	389 (3.5)	0.49	<5 (<3.4)	9 (6.1)	0.08
Clindamycin	36 (10.1)	1,091 (9.8)	0.83	15 (10.2)	18 (12.2)	0.58
Daptomycin	33 (9.3)	1,365 (12.3)	0.09	11 (7.5)	24 (16.3)	0.02
Extended-spectrum cephalosporins	117 (33.0)	4,407 (39.6)	0.01	51 (34.7)	60 (40.8)	0.28
Fluoroquinolones	89 (25.1)	3,248 (29.2)	0.09	41 (27.9)	47 (32.0)	0.44
Gentamicin*	17 (4.8)	626 (5.6)	0.50	9 (6.1)	3 (2.0)	0.08
Linezolid	16 (4.5)	710 (6.4)	0.15	8 (4.4)	13 (8.8)	0.26
Minocycline	<5 (<1.4)	73 (0.7)	1.0	0.0	0.0	NA[d]
Narrow-spectrum cephalosporins*	128 (36.1)	3,468 (31.1)	0.05	50 (34.0)	46 (31.3)	0.62
Piperacillin-tazobactam	197 (55.5)	6,065 (54.4)	0.69	74 (50.3)	81 (55.1)	0.41
Antistaphylococcal penicillins*	84 (23.7)	2,737 (24.6)	0.70	36 (24.5)	31 (21.1)	0.49
Sulfamethoxazole-trimethoprim*	9 (2.5)	623 (5.6)	0.01	6 (4.1)	<5 (<3.4)	0.12
Tetracycline	22 (6.2)	473 (4.2)	0.07	9 (6.1)	<5 (<3.4)	0.08
Tigecycline	<5 (<1.4)	58 (0.5)	1.0	<5 (<3.4)	<5 (<3.4)	1.0
Vancomycin	340 (95.8)	10,625 (95.3)	0.70	139 (94.6)	142 (96.6)	0.39

[a]Data are number (percent) unless otherwise indicated. IQR, interquartile range. Categorical variables were compared using chi-square or Fisher's exact test where appropriate, means were compared using *t* tests, and medians were compared using nonparametric Wilcoxon tests. Asterisks indicate variables included in propensity score. The propensity score included all variables with an asterisk in addition to a facility indicator. Full lists of variables included in the propensity score are also presented in the footnotes to Table 2 and Table S1.

[b]Any contraindication (coagulation disorders, coronary artery bypass graft and heart vessel operations [procedure], general hemorrhage, intracranial/cerebrovascular hemorrhage and stroke, gastrointestinal hemorrhage, other hemorrhage).

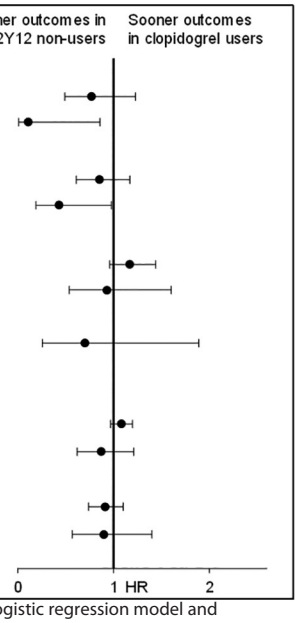
[c]Any indication (ischemic heart disease, arteriosclerosis, peripheral vascular disease, arterial thrombus and thrombosis and atheroembolism, chest pain, other thrombus, percutaneous coronary intervention [procedure], cardiac catheterization [procedure]).

[d]Not mutually exclusive as patients may have had positive *S. aureus* cultures from multiple culture sites. NA, not applicable.

differences in any of the clinical outcomes evaluated were noted between clopidogrel users and P2Y12 inhibitor nonusers among the propensity score-matched cohort (Tables S2 to S4), including 30-day mortality in patients with baseline platelet counts of ≥100,000/μL (HR, 0.56 [95% CI, 0.25 to 1.27]), MSSA infection (HR, 0.38 [95% CI, 0.10 to 1.41]), and MRSA infection (HR, 0.20 [95% CI, 0.02 to 1.71]).

TABLE 2 Clinical outcomes among clopidogrel users compared with P2Y12 inhibitor nonusers in the overall and propensity score matched cohorts[a]

Outcomes	No.of events/No.of patients (%)		HR (95% CI)
	P2Y12 users	Non-users	
Inpatient mortality			
Unadjusted	18/355 (5.1)	875/11,144 (7.9)	0.77 (0.49-1.23)
Propensity Matched	4/147 (2.7)	16/147 (10.9)	**0.11 (0.01-0.86)**
30-day mortality			
Unadjusted	37/355 (10.4)	1,351/11,144 (12.1)	0.85 (0.61-1.17)
Propensity Matched	13/147 (8.8)	22/147 (15.0)	**0.43 (0.19-0.98)**
30-day readmission			
Unadjusted	96/337 (28.5)	2,546/10,269 (24.8)	1.17 (0.96-1.44)
Propensity Matched	34/143 (23.8)	34/131 (26.0)	0.93 (0.54-1.60)
30-day *S. aureus* reinfection			
Unadjusted	4/337 (1.2)	173/10,269 (1.7)	0.70 (0.26-1.89)
Propensity Matched	2/143 (1.4)	0/131 (0.0)	--
Microbiological clearance*			
Unadjusted	338/341 (99.1)	10,353/10,533 (98.3)	1.08 (0.97-1.20)
Propensity Matched	139/141 (98.6)	135/138 (97.8)	0.87 (0.62-1.21)
Thrombocytopenia†			
Unadjusted	101/318 (31.8)	3,729/10,157 (36.7)	0.91 (0.74-1.10)
Propensity Matched	47/144 (32.6)	56/147 (38.1)	0.90 (0.57-1.40)



[a]Bolded indicates *P* value of <0.05. The propensity score was derived from an unconditional logistic regression model and controlled for the variables listed below and in Table S1. In the matched analysis, Cox proportional hazard models controlled for current acute renal failure and history of peripheral and visceral atherosclerosis. Variables in the propensity score model included age, antibiotic use 30 days prior to admission, aspirin use during admission, baseline platelet count, body mass index, concomitant *Escherichia coli*, concomitant *Klebsiella*, contraindication (coagulation disorders, coronary artery bypass graft and heart vessel operations [procedure], general hemorrhage, intracranial/cerebrovascular hemorrhage and stroke, gastrointestinal hemorrhage, other hemorrhage), culture site of *Staphylococcus aureus*, current acute renal failure, fever, intensive care admission, pneumonia, respiratory failure, septicemia, *Escherichia coli* year prior to admission, Elixhauser score, ethnicity, facility indicator, indication (ischemic heart disease, arteriosclerosis, peripheral vascular disease, arterial thrombus and thrombosis and atheroembolism, chest pain, other [thrombus], percutaneous coronary intervention [procedure], cardiac catheterization [procedure]), intensive care admission 30 days before admission, oseltamivir during admission, sex, hospital admission 30 days prior to admission, marital status, methicillin-susceptible/resistant *Staphylococcus aureus*, nursing home admission 30 days prior to admission, other infection in the previous year, race, *Staphylococcus aureus* infection in the previous year, source of admission, statins use 30 days prior to admission, statin use during admission, surgery 30 days prior to admission, time to culture collection from admission, treatment with ampicillin-sulbactam, antistaphylococcal penicillin, gentamicin, narrow-spectrum cephalosporin, or sulfamethoxazole-trimethoprim during admission, treating specialty, year of admission, and history of abdominal hernia, abdominal pain, acute cerebrovascular disease, acute myocardial infarction, acute renal failure, administrative/social admission, adverse effects of medical drugs, alcohol-related disorders, aortic and peripheral arterial embolism or thrombosis, aortic/peripheral/and visceral artery aneurysms, appendicitis, aspiration, asthma, bacterial infection, biliary tract disease, cancer, cardiac dysrhythmias, cerebrovascular disease, chronic obstructive pulmonary disease, chronic ulcer of skin, coagulation and hemorrhagic disorders, complication of device/implant or graft, conduction disorders, congestive heart failure/nonhypertensive, coronary atherosclerosis and other heart disease, diabetes, diverticulosis and diverticulitis, epilepsy/convulsions, essential hypertension, fracture of upper limb, gangrene, gastritis and duodenitis, gastrointestinal hemorrhage, heart valve disorders, hemorrhoids, hepatitis, hypertension with complications and secondary hypertension, joint disorders and dislocations/trauma related, lymphadenitis, mental health disorders, multiple sclerosis, nausea and vomiting, nephritis/nephrosis/renal sclerosis, noninfectious gastroenteritis, nonspecific chest pain, nutritional deficiencies, occlusion or stenosis of precerebral arteries, open wounds of extremities, oral disease (mouth, teeth, and jaw), other acquired deformities, other circulatory disease, other ear and sense organ disorders, other fractures, other injuries and conditions due to external causes, other male genital disorders, other perinatal conditions, other postcondition care, other skin disorders, other upper respiratory disease, paralysis, Parkinson's disease, peri-, endo-, and myocarditis/cardiomyopathy, peripheral and visceral atherosclerosis, peritonitis and intestinal abscess, personality disorders, pleurisy/pneumothorax/pulmonary collapse, rehabilitation care, respiratory failure/insufficiency/arrest, screening and mental health and substance abuse, shock, skin and subcutaneous tissue infections, skull and face fractures, superficial injury/contusion, transient cerebral ischemia, varicose veins of lower extremity, and vertigo. CI, confidence interval; HR, hazard ratio. *, microbiological clearance was defined as a negative follow-up blood culture. Only includes patients with follow-up blood cultures. †, thrombocytopenia defined as a follow-up platelet count $<150,000/\mu$L. Only includes patients with follow-up platelet counts.

DISCUSSION

We found that among patients with *S. aureus* bacteremia in VA medical centers, those already on P2Y12 inhibitors (specifically clopidogrel as the preferred P2Y12 inhibitor used in the VA) before hospital admission and continued through the initial 5-day period of antibiotic treatment had an 89% lower risk of inpatient mortality and 57% lower risk of 30-day mortality than patients who were not exposed to any P2Y12 inhibitors during the admission or the year prior. These findings build further upon data provided by prior

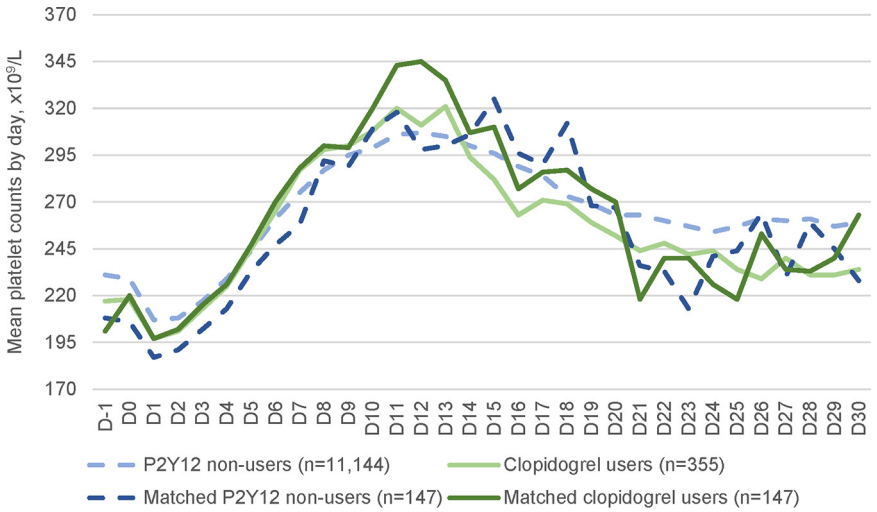


FIG 1 Mean platelet counts by day (D) in the overall and propensity score matched cohorts. For P2Y12 nonusers, values are as follows: day 1, *n* = 9,448, mean = 207, and standard deviation (SD) = 120; day 7, *n* = 6,742, mean = 275, and SD = 152; and day 15, *n* = 2,422, mean = 296, and SD = 167. For clopidogrel users, values are as follows: day 1, *n* = 286, mean = 197, and SD = 92; day 7, *n* = 199, mean = 287, and SD = 119; and day 15, *n* = 53, mean = 282, and SD = 124. For matched P2Y12 nonusers, values are as follows: day 1, *n* = 134, mean = 187, and SD = 96; day 7, *n* = 91, mean = 258, and SD = 122; and day 15, *n* = 26, mean = 325, and SD = 140. For matched clopidogrel users, values are as follows: day 1, *n* = 129, mean = 197, and SD = 97; day 7, *n* = 89, mean = 288, and SD = 124; and day 15, *n* = 22, mean = 310, and SD = 144.

studies that the repurposing of P2Y12 inhibitors in treating *S. aureus* bacteremia should continue to be studied, particularly for the newer agents (4, 5).

Our results are encouraging, as despite appropriate antibiotic therapy, mortality from *S. aureus* bacteremia can still be as high as 10 to 20% (9). Therefore, there is ample room for improved therapy, including adjunctive approaches that attenuate *S. aureus* virulence factor effects on the host and/or enhance innate host immunity against the pathogen. Our results advance recent findings that the P2Y12 inhibitor ticagrelor may augment platelet-mediated killing of *S. aureus* and possibly protect platelets from alpha-toxin-mediated injury and/or accelerated clearance (4, 5). We found positive effects of clopidogrel continuation early in the hospital course on mortality in patients with *S. aureus* bacteremia, when the effect of antimicrobial therapy on reducing inoculum would not yet have taken effect and where alpha-toxin production may be most impactful in driving the clinical presentation. Indeed, pathogen- and infection-specific factors, which we controlled for with propensity score matching, weighs much more heavily on early mortality than later on in patients with *S. aureus* bacteremia (10).

Despite the observed benefit on mortality in *S. aureus* bacteremia with clopidogrel, some additional questions were raised by our study. We observed no differences in risk of thrombocytopenia or in mean platelet counts between clopidogrel users and P2Y12 inhibitor nonusers. Given that P2Y12 inhibitors have been shown to protect platelets from alpha-toxin desialylation and clearance, the benefit of clopidogrel would perhaps have been anticipated to be driven by reduced thrombocytopenia risk and/or higher platelet counts at the time of clinical presentation of *S. aureus* bacteremia in patients taking it (6–8). However, this did not appear to be the case, as clopidogrel users and P2Y12 inhibitor nonusers showed similar drops in platelet counts at admission, achieving a nadir around 48 h and then climbing (Fig. 2). Nevertheless, P2Y12 inhibitors have been shown to directly enhance the platelet-mediated killing of *S. aureus in vitro*, independent of platelet count (4, 5). This enhancement of platelet-driven *S. aureus* killing may play a role in benefiting treatment at the beginning of hospitalization, when platelet counts were observed to drop approximately 20 to 25% in all groups. It was not immediately clear whether the benefit on clinical outcomes in

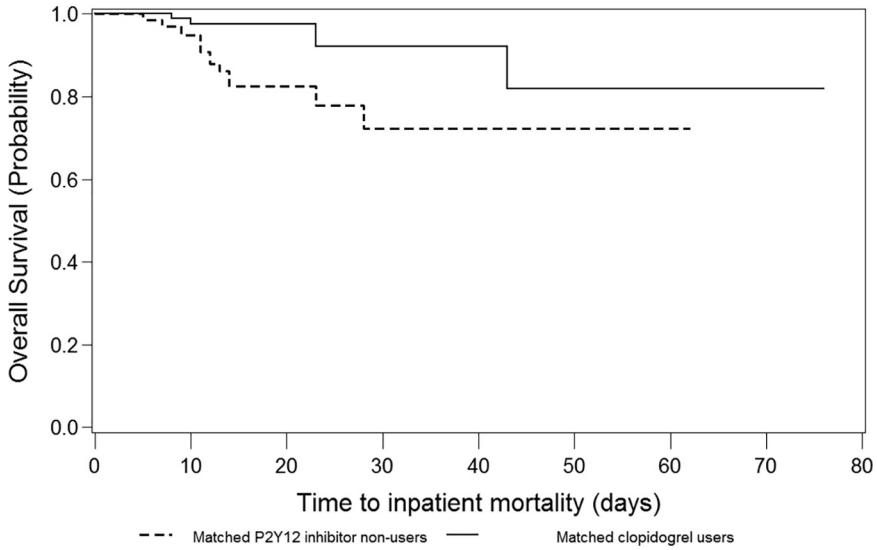


FIG 2 Kaplan-Meier survival curve of inpatient mortality in the propensity score-matched cohort.

clopidogrel users compared with P2Y12 inhibitor nonusers seen would persist beyond the hospitalization, as there was no difference in readmission and reinfection at 30 days between groups. It may be possible that initial protective effects wane, impacting attributable mortality and other clinical outcomes as a direct cause of *S. aureus* bacteremia, which does not continue through to indirect nonattributable causes of death and other outcomes at later time points (9, 11).

We also did not observe any difference in microbiological clearance between the groups. Limited previous work has demonstrated that despite ticagrelor having no direct bactericidal activity, the drug has boosted platelet killing of MSSA at concentrations attainable through standard dosing (4). As such, since in our study there was no difference in thrombocytopenia or in mean platelet counts between the groups, our results related to microbiological clearance correspond with the current literature. Additionally, our findings may be related to the evaluation of chronic clopidogrel use on microbiological clearance, compared to incident, or new, use. In a case report of a patient with a complex MSSA endovascular infection and accompanying thrombocyto-

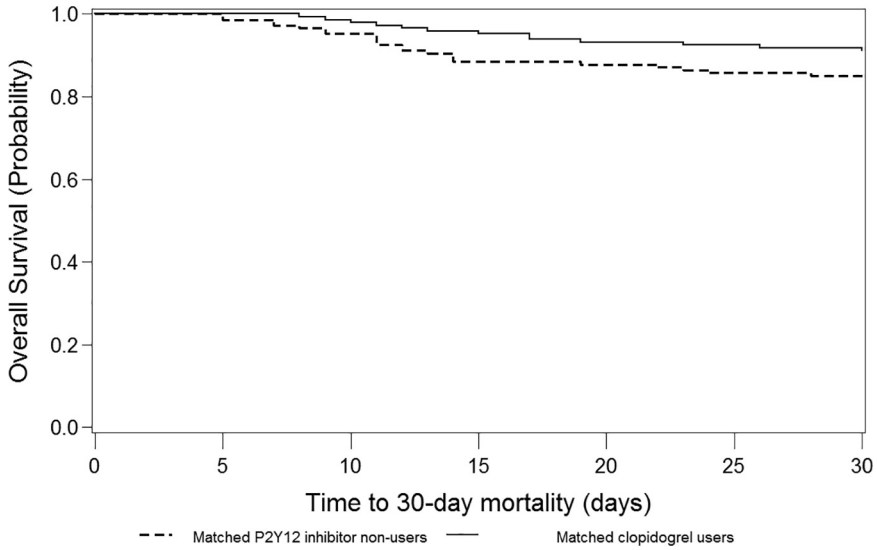


FIG 3 Kaplan-Meier survival curve of 30-day mortality from admission in the propensity score-matched cohort.

penia, the initiation of ticagrelor on day 5 was associated with rapid blood culture clearance the next day and an increase in platelet count into the low normal range (4). Future work should explore whether the therapeutic benefit of PGY12 inhibition on clinical outcomes in patients with *S. aureus* bacteremia is impacted by the timing of initiation of the PGY12 inhibitor (new versus chronic use).

Identifying adjunctive therapies which target *S. aureus* virulence factors or enhance innate immunity in patients with *S. aureus* bacteremia is important, not just to improve patient outcomes but also to increase the understanding of the pathophysiology of the disease, which may lead to novel future therapeutics. Prior studies suggesting that utilizing P2Y12 inhibitors to enhance the innate immune host defense by boosting platelet-mediated *S. aureus* killing are further supported by these findings (4, 5). However, these findings also suggest that study designs must be carefully planned and thought out because P2Y12 inhibitors may not offer benefit to all patients with *S. aureus* bacteremia and, indeed, may perhaps benefit only a small subset of patients. *S. aureus* bacteremia represents a heterogeneous group of infections, the final common pathways of which result in the presence of *S. aureus* in the bloodstream (12). Some infections are based in the vascular system, while others are secondary to invasive infections, such as skin, soft tissue, lung, and other sites (12). *S. aureus* strains themselves differ widely in their production of virulence factors, including alpha-toxin (5). Additionally, there is a growing repertoire of P2Y12 inhibitors of various potencies and pharmacokinetic profiles. This study focused on the older-generation P2Y12 inhibitor clopidogrel, but newer agents, such as ticagrelor or cangrelor, may offer a more robust clinical effect. Cangrelor appears particularly promising in the acute-care setting given its parenteral administration and shorter half-life, a positive attribute if a hemorrhagic complication should emerge and therapy needs to be immediately discontinued (13). While we did not assess hemorrhagic complications, we did not observe a difference in thrombocytopenia between clopidogrel users and nonusers. Future studies should assess hemorrhagic concerns, given the strong possibility of metastatic infection in patients with *S. aureus* bacteremia, particularly to the brain. Given the concern of metastatic infection that may be present in patients with left-sided endocarditis, we would advocate for an initial clinical trial of P2Y12 inhibitors in patients with right-sided endocarditis, especially with concomitant thrombocytopenia in which the host platelet-mediated innate defense against *S. aureus* is highly compromised but particularly relevant and would require therapeutic assistance.

There are some potential downsides to P2Y12 inhibition in the treatment of *S. aureus* bacteremia. Although P2Y12 inhibitors protect platelets from alpha-toxin desialylation and clearance, previous work has demonstrated that cangrelor (a specific P2Y12 antagonist) mitigated the platelet staphylocidal response by blocking platelets from releasing granular antimicrobial peptides (platelet microbicidal proteins and platelet kinocidins) (4, 5, 14). Additionally, alpha-toxin release and lysis of platelets may have a salutary response against *S. aureus* by evoking release of platelet antimicrobial peptides (15).

There are some limitations to our study. The first is that our study cohort included patients with *S. aureus* bacteremia who were already on clopidogrel prior to admission, as opposed to patients in a clinical trial who may be initiated on clopidogrel therapy at the time of *S. aureus* bacteremia diagnosis. We included patients already on clopidogrel, as the inclusion of those newly initiated on P2Y12 inhibitors may introduce selection bias where those started on clopidogrel may have been less sick and/or physicians decided to be more aggressive with antiplatelet therapy in the setting of the central nervous system and/or cardiac diseases or procedures, such as endovascular stents. However, our study cohort of current clopidogrel users may be at different risk for hemorrhagic complications than those newly initiated on clopidogrel in a clinical trial. For example, the initiation of aspirin treatment was trialed in patients with infective endocarditis to reduce embolic risk, based on the knowledge that this metric was significantly reduced in patients already on aspirin at the time of the diagnosis (16). In clinical trials, the addition of aspirin did not reduce the risk of embolic events but actually was

associated with an increased risk of bleeding (16). Moreover, our study cohort also required clopidogrel users to be continued on the drug for at least 5 days after admission, therefore potentially excluding those who may have been doing poorly and had their chronic medications stopped on admission.

Another major concern is the inability to control for all factors that contribute to confounding between patients with *S. aureus* bacteremia receiving clopidogrel versus non-P2Y12 inhibitor users. We used propensity score matching to mitigate the impact of confounding between the treatment groups. While our propensity score included observed and known confounders related to clopidogrel use versus non-P2Y12 use, including demographics, comorbidities, contradictions/indications, concomitant antithrombotic agents, prior health care exposures, and other clinical characteristics, there is the potential for residual confounding due to other unmeasured factors. For example, severity not captured by intensive care treatment, concomitant diagnosis codes, and clinical characteristics or easier-to-clear syndromes, such as peripheral vascular catheter-associated *S. aureus* bacteremia, may cause residual confounding. We could not assess why patients in the comparison group were not on P2Y12 therapy, if indicated, and could also not assess clopidogrel metabolism. Consequently, another interpretation could be that among patients who have the same predicted probability of receiving clopidogrel therapy, actually being on clopidogrel may be protective against mortality in patients who can metabolize clopidogrel. Also, while we matched patients on baseline platelet count, we did not assess mean platelet volume (MPV), which correlates with platelet function and activation. Additionally, we assessed all cause-mortality, and therefore, underlying health status or coinfections may have impacted mortality. However, we did control for underlying conditions and coinfections in the propensity score model. Due to the retrospective nature of our study, we do not have detailed microbial characterization of the *S. aureus* strain, which is a limitation due to the highly heterogeneous nature of *S. aureus* in terms of virulence and toxin production. Additionally, we defined microbiological clearance as a negative follow-up blood culture, but patients may or may not have had a bacterial clearance of infection at their principal site of infection. Finally, the VA population consists primarily of older white males; therefore, the generalizability of this study may be limited.

In summary, this retrospective cohort of VA patients with *S. aureus* bacteremia demonstrated a significant reduction in all-cause mortality in patients receiving P2Y12 inhibitors (clopidogrel). These results build upon prior data showing that the repurposing of P2Y12 inhibitors warrants further study in prospective clinical trials in order to validate these agents as viable adjuncts. Such trials may need to focus on subgroups of *S. aureus* bacteremia patients for whom benefits may outweigh risks, such as those with right-sided endocarditis, presence of thrombocytopenia, or infections by strains with higher alpha-toxin production.

MATERIALS AND METHODS

Data sources. Clinical data on hospitalizations, medical history, and posthospitalization outcomes were obtained from national Veterans Affairs (VA) databases. The study variables were built from demographics data, microbiology and other laboratory data, diagnosis codes (*International Classification of Diseases*, ninth and tenth revisions) (17, 18) from outpatient visits and inpatient stays, and pharmacy data (outpatient and inpatient) (19). This study was approved by the Institutional Review Board and Research and Development Committee of the VA Providence Healthcare System (CIRB-2014-047).

Study design and population. This retrospective cohort study included patients with *S. aureus*-positive blood cultures collected from 1 January 2010 to 1 December 2018 during a hospital admission at a VA medical center. The following inclusion criteria were applied: (i) age of 18 years or older, (ii) hospitalization for more than 2 days, (iii) survival for more than 2 days, and (iv) collection of cultures between 1 day before admission and 1 day after admission. Patients were excluded if they were not on appropriate initial antibiotic therapy within 3 days of the culture collection date, defined as intravenous β-lactam therapy (ampicillin-sulbactam, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftaroline, ceftazidime, ceftriaxone, doripenem, ertapenem, imipenem-cilastatin, meropenem, minocycline, nafcillin, oxacillin, and piperacillin-tazobactam) or ciprofloxacin, clindamycin, daptomycin, doxycycline, gatifloxacin, gentamicin, levofloxacin, linezolid, moxifloxacin, tetracycline, tigecycline, sulfamethoxazole-trimethoprim, or vancomycin for methicillin-susceptible *S. aureus* (MSSA) and ceftaroline, clindamycin, daptomycin, doxycycline, gentamicin, linezolid, minocycline, tetracycline, tigecycline, sulfamethoxazole-trimethoprim, or vancomycin for methicillin-resistant *S. aureus* (MRSA). Patients were also

excluded if the culture was resistant to all initial antibiotic therapies received. In the case of multiple hospital admissions during the study period, only the first admission was selected for analysis.

Exposure. To capture patients already on clopidogrel at the time of *S. aureus* infection and continuing clopidogrel as antibiotic therapy was initiated, we identified patients on clopidogrel for at least 30 days before admission with continued use for at least 5 days after admission. Patients on prasugrel ($n = 5$) and ticagrelor ($n = 9$) were not included in the study due to their low numbers.

P2Y12 inhibitor nonusers included patients without any P2Y12 inhibitor use (clopidogrel, ticlopidine, ticagrelor, prasugrel, or cangrelor) in the year before admission through discharge. Additionally, nonusers included those surviving at least 5 days to correspond with the treatment group.

Outcomes. Outcomes evaluated included time to in-hospital mortality and mortality inside or outside the hospital within 30 days of admission. Mortality was defined as death due to any cause. During the admission, we assessed time to microbiological clearance, defined as a negative follow-up blood culture, among patients with follow-up blood cultures, and time to thrombocytopenia, defined as a follow-up platelet count of $<$150,000/μL, among patients with follow-up platelet counts. Moderate thrombocytopenia was defined as a platelet count of $<$100,000/μL. We also evaluated time to *S. aureus* reinfection and readmission within 30 days of hospital discharge.

Covariates. Covariates evaluated included demographics, clinical characteristics, and medical history (Table 1). Clinical characteristics and medical history consisted of any indications or contraindications for P2Y12 use, current treatment specialty, source of admission, antibiotic treatment, the timing of culture collection from admission, concomitant medications with antiplatelet activity, such as aspirin and statins, and adjunctive therapies that may improve patient outcomes, such as oseltamivir (5), previous health care exposures, antibiotic exposures, and infections, coinfections with other organisms, comorbidities in the prior year, and comorbidity burden (Elixhauser score).

Statistical analyses. Differences in demographics, clinical characteristics, and medical history were compared between clopidogrel users and P2Y12 inhibitor nonusers using chi-square or Fisher exact test for categorical variables and *t* test or Wilcoxon rank sum test for continuous variables. Propensity scores were developed for exposure to clopidogrel users compared with P2Y12 inhibitors, as a function of all known confounders and potential confounders associated with exposure and clinical outcomes (8, 10). Likelihood ratio testing was used to identify variables independently associated with both exposure and clinical outcomes. Propensity scores were developed using unconditional logistic regression with manual backward stepwise elimination and assessed for the absence of multicollinearity and goodness of fit. We matched clopidogrel users to P2Y12 inhibitor nonusers on their propensity score using nearest-neighbor matching within a caliper of 0.0001. We assessed absolute standardized differences before and after matching to assess balance of potential confounders (20). Common support of the propensity score was assessed visually (20, 21). Unadjusted and matched hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard regression models. Any variable with an absolute standardized difference greater than 0.2 after matching was assessed in the Cox model and retained if statistically significant. We conducted stratified analyses by baseline platelet count and MRSA/MSSA status. SAS software v.9.2 (SAS Institute, Cary, NC) was used for all analyses.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

ACKNOWLEDGMENTS

The views expressed are those of the authors and do not necessarily reflect the position or policy of the U.S. Department of Veterans Affairs. This material is based upon work supported, in part, by the Office of Research and Development, Department of Veterans Affairs.

This work was unfunded.

Aisling R. Caffrey has received research funding from AbbVie, Gilead, Merck, Pfizer, and Shionogi and has received speaking honoraria from Merck. Kerry L. LaPlante has received research funding from AbbVie, Gilead, Merck, Pfizer, and Shionogi. George Sakoulas has received consulting and speaking honoraria from Abbvie and Paratek.

REFERENCES

1. Thomer L, Schneewind O, Missiakas D. 2016. Pathogenesis of Staphylococcus aureus bloodstream infections. Annu Rev Pathol 11:343–364. https://doi.org/10.1146/annurev-pathol-012615-044351.
2. Fowler VG, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, Corey GR, Spelman D, Bradley SF, Barsic B, Pappas PA, Anstrom KJ, Wray D, Fortes CQ, Anguera I, Athan E, Jones P, van der Meer JTM, Elliott TSJ, Levine DP, Bayer AS, ICE Investigators. 2005. Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA 293:3012–3021. https://doi.org/10.1001/jama.293.24.3012.
3. Ford CA, Hurford IM, Cassat JE. 2020. Antivirulence strategies for the treatment of Staphylococcus aureus infections: a mini review. Front Microbiol 11:632706. https://doi.org/10.3389/fmicb.2020.632706.
4. Ulloa E, Uchiyama S, Gillespie R, Nizet V, Sakoulas G. 2021. Ticagrelor increases platelet-mediated Staphylococcus aureus killing resulting in

clearance of bacteremia. J Infect Dis 224:1566–1569. https://doi.org/10.1093/infdis/jiab146.
5. Sun J, Uchiyama S, Olson J, Morodomi Y, Cornax I, Ando N, Kohno Y, Kyaw MMT, Aguilar B, Haste NM, Kanaji S, Kanaji T, Rose WE, Sakoulas G, Marth JD, Nizet V. 2021. Repurposed drugs block toxin-driven platelet clearance by the hepatic Ashwell-Morell receptor to clear. Sci Transl Med 13:eabd6737. https://doi.org/10.1126/scitranslmed.abd6737.
6. Fuller R, Chavez B. 2012. Ticagrelor (Brilinta), an antiplatelet drug for acute coronary syndrome. P T 37:562–568.
7. Yeaman MR. 2014. Platelets: at the nexus of antimicrobial defence. Nat Rev Microbiol 12:426–437. https://doi.org/10.1038/nrmicro3269.
8. Gafter-Gvili A, Mansur N, Bivas A, Zemer-Wassercug N, Bishara J, Leibovici L, Paul M. 2011. Thrombocytopenia in Staphylococcus aureus bacteremia: risk factors and prognostic importance. Mayo Clin Proc 86:389–396. https://doi.org/10.4065/mcp.2010.0705.
9. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. 2012. Predictors of mortality in Staphylococcus aureus bacteremia. Clin Microbiol Rev 25:362–386. https://doi.org/10.1128/CMR.05022-11.
10. Bassetti M, Peghin M, Trecarichi EM, Carnelutti A, Righi E, Del Giacomo P, Ansaldi F, Trucchi C, Alicino C, Cauda R, Sartor A, Spanu T, Scarparo C, Tumbarello M. 2017. Characteristics of Staphylococcus aureus bacteraemia and predictors of early and late mortality. PLoS One 12:e0170236. https://doi.org/10.1371/journal.pone.0170236.
11. Thorlacius-Ussing L, Sandholdt H, Larsen AR, Petersen A, Benfield T. 2019. Age-dependent increase in incidence of Staphylococcus aureus bacteremia, Denmark, 2008–2015. Emerg Infect Dis 25:875–882. https://doi.org/10.3201/eid2505.181733.
12. Rose W, Fantl M, Geriak M, Nizet V, Sakoulas G. 2021. Current paradigms of combination therapy in methicillin-resistant Staphylococcus aureus (MRSA) bacteremia: does it work, which combination and for which patients? Clin Infect Dis 73:2353–2360. https://doi.org/10.1093/cid/ciab452.
13. Chiesi USA, Inc. 2020. Cangrelor prescribing information. https://resources.chiesiusa.com/Kengreal/KENGREAL_US_PI.pdf.
14. Trier DA, Gank KD, Kupferwasser D, Yount NY, French WJ, Michelson AD, Kupferwasser LI, Xiong YQ, Bayer AS, Yeaman MR. 2008. Platelet antistaphylococcal responses occur through P2X1 and P2Y12 receptor-induced activation and kinocidin release. Infect Immun 76:5706–5713. https://doi.org/10.1128/IAI.00935-08.
15. Bayer AS, Ramos MD, Menzies BE, Yeaman MR, Shen AJ, Cheung AL. 1997. Hyperproduction of alpha-toxin by Staphylococcus aureus results in paradoxically reduced virulence in experimental endocarditis: a host defense role for platelet microbicidal proteins. Infect Immun 65:4652–4660. https://doi.org/10.1128/iai.65.11.4652-4660.1997.
16. Chan K-L, Dumesnil JG, Cujec B, Sanfilippo AJ, Jue J, Turek MA, Robinson TI, Moher D, Investigators of the Multicenter Aspirin Study in Infective Endocarditis. 2003. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol 42:775–780. https://doi.org/10.1016/s0735-1097(03)00829-5.
17. Clinical Classifications Software (CCS). 2017. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD.
18. Clinical Classifications Software Refined (CCSR). 2021. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp.
19. Rajeevan N, Niehoff KM, Charpentier P, Levin FL, Justice A, Brandt CA, Fried TR, Miller PL. 2017. Utilizing patient data from the veterans administration electronic health record to support web-based clinical decision support: informatics challenges and issues from three clinical domains. BMC Med Inform Decis Mak 17:111. https://doi.org/10.1186/s12911-017-0501-x.
20. Stuart EA. 2010. Matching methods for causal inference: a review and a look forward. Stat Sci 25:1–21. https://doi.org/10.1214/09-STS313.
21. Vaughan AS, Kelley CF, Luisi N, del Rio C, Sullivan PS, Rosenberg ES. 2015. An application of propensity score weighting to quantify the causal effect of rectal sexually transmitted infections on incident HIV among men who have sex with men. BMC Med Res Methodol 15:25. https://doi.org/10.1186/s12874-015-0017-y.