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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. Several 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 (2010-2018) 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 five 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 non-users (n=147 propensity score-matched pairs): inpatient mortality hazard ratio (HR) 0.11, 95% confidence interval (CI) 0.01-0.86, and 30-day mortality HR 0.43, 95% CI 0.19-0.98. 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.

Introduction

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 heterogenous 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 adenosine diphosphate 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 anti-thrombotic agent used to prevent cardiovascular events in patients with acute coronary syndrome or a history of myocardial infarction, such as in patients receiving percutaneous coronary intervention (PCI) (5). Recent evidence suggests 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 not on P2Y12 inhibitors. We selected clopidogrel as the exposure of interest, as it was the predominant P2Y12 inhibitor (>96%) utilized among the cohort of patients with *S. aureus* bacteremia in the VA Healthcare System during our study period.

Materials and Methods

Data Sources

Clinical data on hospitalizations, medical history, and post-hospitalization 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) from outpatient visits and inpatient stays, and pharmacy data (outpatient and inpatient) (9). 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 January 1, 2010, to December 1, 2018, during a hospital admission at a VA medical center. The following inclusion criteria were applied: (1) aged 18 years old or older, (2) hospitalized for more than two days, (3) survived for more than two days, and (4) cultures collected between one day before admission or one day after admission. Patients were excluded if they were not on appropriate initial antibiotic therapy within three 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 five days after admission. Patients on prasugrel (n=5) and ticagrelor (n=9) were not included in the study due to these low numbers.

P2Y12 inhibitor non-users included patients without any P2Y12 inhibitor use (clopidogrel, ticlopidine, ticagrelor, prasugrel, cangrelor) in the year before admission through discharge. Additionally, non-users included those surviving at least five 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 <150,000/μL, among patients with follow-up platelet counts. Moderate thrombocytopenia was defined as a platelet count <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 healthcare 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 non-users 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 multi-collinearity and goodness of fit. We matched clopidogrel users to P2Y12 inhibitor non-users 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.(11) Common support of the propensity score was assessed visually.(11, 12) 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.

Results

Our VA-based study included 355 clopidogrel users and 11,144 non-users, all with *S. aureus* bacteremia, with mean respective ages of 69 (+/- 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 Supplemental Table 1. Propensity scores of the clopidogrel users and non-users demonstrated complete overlap (Supplemental Figure 1: 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 Supplemental Table 1.

Platelet Counts

There were no differences in mean platelet counts between clopidogrel users and P2Y12 inhibitor non-users at the time of hospital admission in both the overall and propensity score-matched cohorts. The median platelet count was similar in clopidogrel users (206,000/μL, interquartile range [IQR]149,000-283,000) and P2Y12 inhibitor non-users (212,000/μL, IQR 146,000-296,000, p=0.42) in the overall cohort. Figure 1 displays the similar mean daily platelet counts during admission for clopidogrel users and P2Y12 inhibitor non-users in the overall and propensity score-matched cohorts. Clopidogrel users and P2Y12 inhibitor non-users both demonstrated a nadir in the first 48 hours after hospitalization, followed by a steady rise peaking at 10-14 days, and mild decline hitting a plateau at three 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 non-users. 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: inpatient mortality hazard ratio (HR) 0.11, 95% confidence interval (CI) 0.01-0.86, and 30-day mortality HR 0.43, 95% CI 0.19-0.98. Kaplan-Meier survival curve of inpatient mortality and 30-day mortality in the propensity score matched cohort are presented

in Figures 2 and 3. There were no other significant differences in clinical outcomes, including microbiological clearance (HR 0.87, 95% CI 0.62-1.21) or thrombocytopenia (HR 0.90, 95% CI 0.57-1.40) during the admission or readmission (HR 0.93, 95% CI 0.54-1.60). 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 non-users. In the stratified analyses by baseline platelet count and MSSA/MRSA, no statistically significant differences in any of the clinical outcomes evaluated were noted between clopidogrel users and P2Y12 inhibitor non-users among the propensity score-matched cohort (Supplemental Tables 2-4), including 30-day mortality in patients with baseline platelet count ≥100,000/μL (HR 0.56, 95% 0.25- 1.27), MSSA infection (HR 0.38, 95% 0.10- 1.41), and MRSA infection (HR 0.20, 95% 0.02- 1.71).

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 studies that the repurposing of P2Y12 inhibitors in treating *S. aureus* bacteremia should continue to be studied, particularly 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 10-20% (13). 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 compared to 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 non-users. 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 both clopidogrel users and P2Y12 inhibitor non-users showed a similar drop in platelet counts at admission, achieving a nadir around 48 hours and then climbing (Figure 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, where platelet counts were observed to drop approximately 20-25% in all groups. It was not immediately clear whether the benefit on clinical outcomes in clopidogrel users compared with P2Y12 inhibitor non-users 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 non-attributable causes of death and other outcomes at later time points (13, 15).

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, as compared to incident, or new, use. In a case report of a patient with a complex MSSA endovascular infection and accompanying thrombocytopenia, 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 that may lead to novel future therapeutics. Prior studies suggest 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 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, perhaps in only a small subset of patients. *S. aureus*

bacteremia represents a heterogenous group of infections, the final common pathways of which result in the presence of *S. aureus* in the bloodstream (16). Some infections are based in the vascular system, while others are secondary to invasive infections, such as skin, soft tissue, lung, and other sites (16). *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 varying potency 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 entertaining 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 (17). While we did not assess hemorrhagic complications, we did not observe a difference in thrombocytopenia between clopidogrel users and non-users. 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 where 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 platelet staphylocidal response by blocking platelets from releasing granular-based antimicrobial peptides (platelet microbicidal proteins and platelet kinocidins).(4, 5, 18) Additionally, alpha-toxin release and lysis of platelets may have a salutary response against *S. aureus* by evoking release of platelet antimicrobial peptides.(19)

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.(20) 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.(20) 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 healthcare 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. As such, 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 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 subgroup(s) of *S. aureus* bacteremia patients where benefits may outweigh risks, such as those with right-sided endocarditis, presence of thrombocytopenia, or infections by strains with higher alpha-toxin production.

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Tables

Table 1. Baseline demographics and patient characteristics among clopidogrel users compared with P2Y12 inhibitor non-users in the overall and propensity score matched cohorts

Patient characteristics	Overall clopidogrel users (n=355)	Overall P2Y12 inhibitor non-users (n=11,144)	P-value	Matched clopidogrel users (n=147)	Matched P2Y12 inhibitor non-users (n=147)	P-value
Age (years), 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*	24 (6.8%)	848 (7.6%)	0.55	11 (7.5%)	14 (9.5%)	0.53
Married*	158 (44.5%)	4,340 (38.9%)	0.03	66 (44.9%)	64 (43.5%)	0.81
Year of admission* 2010-2012 2013-2015 2016-2018	 102 (28.7%) 121 (34.1%) 132 (37.2%)	 4,148 (37.2%) 3,526 (31.6%) 3,470 (31.1%)	0.003	 47 (32.0%) 43 (29.3%) 57 (38.8%)	 42 (28.6%) 47 (32.0%) 58 (39.5%)	0.79
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	142 (40.0%)	4,715 (42.3%)	0.39	50 (34.0%)	58 (39.5%)	0.33

other culture sites						
Skin and soft tissue*						
Urine*	87 (24.5%)	1,910 (17.1%)	0.0003	24 (16.3%)	32 (21.8%)	0.23
Respiratory						
Bone joint*	29 (8.2%)	1,504 (13.5%)	0.004	17 (11.6%)	7 (4.8%)	0.03
Other	11 (3.1%)	559 (5.0%)	0.10	<5 (<3.4%)	8 (5.4%)	0.24
	11 (3.1%)	590 (5.3%)	0.07	7 (4.8%)	7 (4.8%)	1.0
	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						
Hospital	167 (47.0%)	5,113 (45.9%)	0.66	72 (49.0%)	65 (44.2%)	0.41
Nursing home	2 (0.6%)	67 (0.6%)	1.0	<5 (<3.4%)	<5 (<3.4%)	0.49
	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

Healthcare 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*,**	221 (62.3%)	4,418 (39.6%)	<0.0001	77 (52.4%)	71 (48.3%)	0.48
Indication*,***	311 (87.6%)	4,644 (41.7%)	<0.0001	111 (75.5%)	107 (72.8%)	0.59
Medical history, previous year	75 (21.1%)	810 (7.3%)	<0.0001	33 (22.5%)	28 (19.1%)	0.47
Acute cerebrovascular disease*						
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
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*						
Diabetes*						

Infective arthritis/ osteomyelitis*	158 (44.5%)	2,183 (19.6%)	<0.0001	48 (32.7%)	52 (35.4%)	0.62
Liver disease	273 (76.9%)	5,968 (53.6%)	<0.0001	103 (70.1%)	102 (69.4%)	0.90
Hypertension*	67 (18.9%)	1,392 (12.5%)	0.0004	22 (15.0%)	19 (12.9%)	0.61
Peripheral visceral atherosclerosis*	43 (12.1%)	1,672 (15.0%)	0.13	17 (11.6%)	14 (9.5%)	0.57
Pneumonia	323 (91.0%)	7,888 (70.8%)	<0.0001	129 (87.8%)	129 (87.8%)	1.0
Respiratory failure*	163 (45.9%)	1,787 (16.0%)	<0.0001	48 (32.7%)	32 (21.8%)	0.04
Septicemia						
Shock*	64 (18.0%)	1,619 (14.5%)	0.07	24 (16.3%)	20 (13.6%)	0.51
Skin and soft tissue	40 (11.3%)	997 (9.0%)	0.13	11 (7.5%)	15 (10.2%)	0.41
infection*	54 (15.2%)	1,696 (15.2%)	0.99	21 (14.3%)	26 (17.7%)	0.43
	7 (2.0%)	264 (2.4%)	0.63	<5 (<3.4%)	<5 (<3.4%)	1.0
	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 year	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 year						
Aspirin						
Statin	109 (30.7%)	1,599 (14.4%)	<0.0001	31 (21.1%)	33 (22.5%)	0.78
Oseltamivir	167 (47.0%)	2,258 (20.3%)	<0.0001	52 (35.4%)	59 (40.1%)	0.40
	<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						
Ceftaroline	34 (9.6%)	1,264 (11.3%)	0.30	11 (7.5%)	12 (8.2%)	0.83
Clindamycin	10 (2.8%)	389 (3.5%)	0.49	<5 (<3.4%)	9 (6.1%)	0.08
Daptomycin	36 (10.1%)	1,091 (9.8%)	0.83	15 (10.2%)	18 (12.2%)	0.58

Extended spectrum	33 (9.3%)	1,365 (12.3%)	0.09	11 (7.5%)	24 (16.3%)	0.02
cephalosporins	117 (33.0%)	4,407 (39.6%)	0.01	51 (34.7%)	60 (40.8%)	0.28
Fluoroquinolones						
Gentamicin*						
Linezolid	89 (25.1%)	3,248 (29.2%)	0.09	41 (27.9%)	47 (32.0%)	0.44
Minocycline	17 (4.8%)	626 (5.6%)	0.50	9 (6.1%)	3 (2.0%)	0.08
Narrow spectrum	16 (4.5%)	710 (6.4%)	0.15	8 (4.4%)	13 (8.8%)	0.26
cephalosporins*	<5 (<1.4%)	73 (0.7%)	1.0	--	--	--
Piperacillin-tazobactam	128 (36.1%)	3,468 (31.1%)	0.05	50 (34.0%)	46 (31.3%)	0.62
Antistaphylococcal						
penicillins*	197 (55.5%)	6,065 (54.4%)	0.69	74 (50.3%)	81 (55.1%)	0.41
Sulfamethoxazole-						
trimethoprim*	84 (23.7%)	2,737 (24.6%)	0.70	36 (24.5%)	31 (21.1%)	0.49
Tetracycline						
Tigecycline	9 (2.5%)	623 (5.6%)	0.01	6 (4.1%)	<5 (<3.4%)	0.12
Vancomycin						
	22 (6.2%)	473 (4.2%)	0.07	9 (6.1%)	<5 (<3.4%)	0.08
	<5 (<1.4%)	58 (0.5%)	1.0	<5 (<3.4%)	<5 (<3.4%)	1.0
	340 (95.8%)	10,625 (95.3%)	0.70	139 (94.6%)	142 (96.6%)	0.39

Data are n (%), unless otherwise indicated. SD = standard deviation, IQR = interquartile range. Categorical variables were compared using chi-square or Fisher's exact tests where appropriate, means were compared using t-tests, and medians were compared using non-parametric Wilcoxon tests.

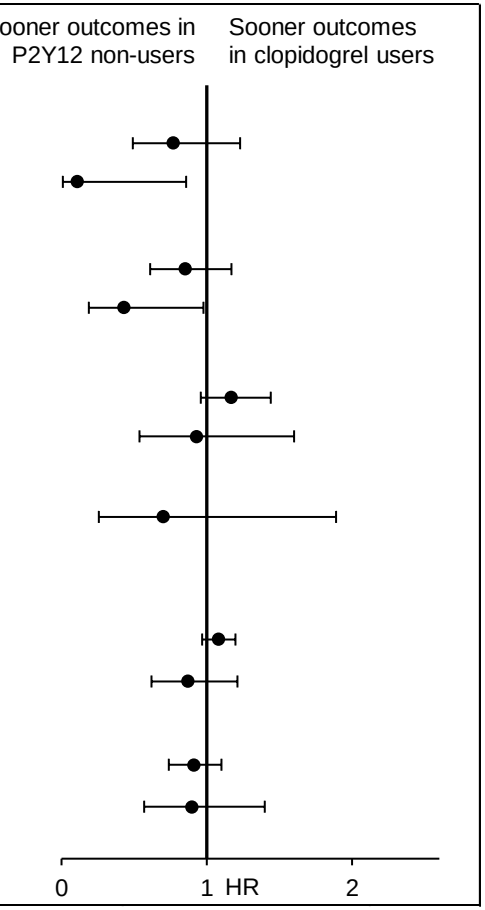
*Variable included in propensity score. Propensity score included all variables with an * in addition to a facility indicator. Full list of variables included in the propensity score are also presented in the footnote of Table 2 and Supplemental Table 1.

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

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

Table 2. Clinical outcomes among clopidogrel users compared with P2Y12 inhibitor non-users in the overall and propensity score matched cohorts

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)



CI=confidence interval; HR=hazard ratio.

Bolded indicates p-value <0.05. The propensity score was dervied from an uncoditional logistic regression model and controlled for the variables listed below and in Supplemental Table 1. In the matched analysis, Cox proportional hazards models controlled for current acute renal failure, and history of peripheral and visceral atherosclerosis.

Variables in the propensity score model: age, antibiotic use 30 days prior to admission, aspirin use during admission, baseline platelet count, body mass index, concomitant *Escherichia coli*, concomitant K*lebsiella,* contraindication (coagulation disorders, coronary artery bypass graft & heart vessel operations [procedure], general hemorrhage, intracranial/cerebrovascular hemorrhage & 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 & thrombosis & atheroembolism, chest pain, other (thrombus), percutaneous coronary intervention [procedure], cardiac catheterization [procedure]), intensive care admission 30 day 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 day prior to admission, time to culture collection from admission, treated with ampicillin-sulbactam, anti-staphylococcal 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/non-hypertensive, 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 post-condition 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.

*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/uL. Only includes patients with follow-up platelet counts.

Figures

Figure 1. Mean platelet counts by day in the overall and propensity score matched cohorts

Footnote: P2Y12 non-users: Day 1, n=9,448, mean=207, standard deviation (sd)=120. Day 7, n=6,742, mean=275, sd=152. Day 15, n=2,422, mean=296, sd=167.
Clopidogrel users: Day 1, n=286, mean=197, sd=92. Day 7, n=199, mean=287, sd=119. Day 15, n=53, mean=282, sd=124.
Matched P2Y12 non-users: Day 1, n=134, mean=187, sd=96. Day 7, n=91, mean=258, sd=122. Day 15, n=26, mean=325, sd=140.
Matched clopidogrel users: Day 1, n=129, mean=197, sd=97. Day 7, n=89, mean=288, sd=124. Day 15, n=22, mean=310, sd=144.

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

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