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Anti-platelet therapy significantly reduces inpatient mortality in patients with *Staphylococcus aureus* bacteremia

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ABSTRACT

Background: There is a growing body of evidence which suggests that P2Y12 inhibitors may have antibacterial properties in vivo. To our knowledge, this has not been previously examined using real world clinical data from patients with specific infections.

Methods: Our retrospective cohort study included patients admitted to Veterans Affairs hospitals between 2010-2018 with blood cultures positive for *S. aureus* and treated with appropriate antibiotics within 48 hours of culture collection. We included patients treated with clopidogrel for at least the 30 days prior to admission and continued use for at least 5 days after admission. Non-users included patients without P2Y12 inhibitor use in the year prior to admission through discharge. We compared clinical outcomes during the *S. aureus* bacteremia admission among clopidogrel users and non-users using propensity score matched Cox proportional hazards regression models.

Results: We identified 357 clopidogrel users and 13,298 non-users. Mean age was 70 years and 66 years, respectively. Over 97% were male in both the groups, and the overall inpatient mortality rate was 8.7%. We were able to match 288 users and non-users, which were well matched in terms of baseline covariates. Inpatient mortality was significantly lower among clopidogrel users (hazard ratio [HR] 0.20, 95% confidence interval [CI] 0.04-0.91), and 30-day mortality was non-significantly lower (HR 0.84, 95% CI 0.50-1.41). There was no difference between the groups in readmission or re-infection within 30 days of discharge.

Conclusions: Among patients with *S. aureus* bacteremia, those treated with clopidogrel in the days leading up to admission and continuing through the initial period of antibiotic treatment, had an 80% lower risk of inpatient mortality. Identifying adjunctive therapies which improve clinical outcomes among patients with *S. aureus* bacteremia is highly important in order to improve patient outcomes and to increase the understanding of the pathophysiology of the disease. Prospective clinical studies are needed to further define the potential benefits of P2Y12 inhibitors in *S. aureus* bacteremia and possibly other infection types.

***Due to low numbers, updated to exclude prasugrel (n=5) and ticagrelor (n=9).**

BACKGROUND

High alpha-toxin strains have been associated with low platelet counts and mortality in *S. aureus* bacteremia. Platelets may have a key role in protecting against death in *S. aureus* bacteremia, and P2Y12 inhibitors protect platelets from alpha-toxin toxicity.

OBJECTIVES

To assess the impact of clopidogrel on clinical outcomes in patients hospitalized with *S. aureus* bacteremia.

METHODS

Included patients hospitalized in Veterans Affairs Medical Centers with *S. aureus* positive blood cultures, Jan 2010-Dec 2018). Positive cultures were collected the day prior to admission until one day after admission. Patients were excluded if death or discharge occurred on the day of admission or the next day, or initial antibiotic therapy was inappropriate for treating methicillin susceptible or resistant *S. aureus* (based on the antibiotic or resistance). Clopidogrel users and non-users were matched on propensity scores, and time to event analyses utilized Cox models.

RESULTS

Patient characteristics	Clopidogrel users (n=288)	Matched non-users (n=288)
Age (years), mean (SD)	69.7 (10.4)	69.6 (11.7)
Male	286 (99.3%)	285 (99.0%)
White	218 (75.7%)	219 (76.0%)
Methicillin-resistant	100 (34.7%)	110 (38.2%)
Treating specialty intensive care	103 (35.8%)	103 (35.8%)
Hospitalization 30 days prior to admission	64 (22.2%)	48 (16.7%)
Baseline platelet count, median (IQR)	210 (146-289)	207 (156-287)
Elixhauser, median (IQR)	6 (4-8)	5 (4-7)
Infections in the previous year	117 (40.6%)	123 (42.7%)
S. aureus in other culture sites	109 (37.9%)	108 (37.5%)
Co-infections	58 (20.1%)	70 (24.3%)

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. No significant differences between the matched groups.

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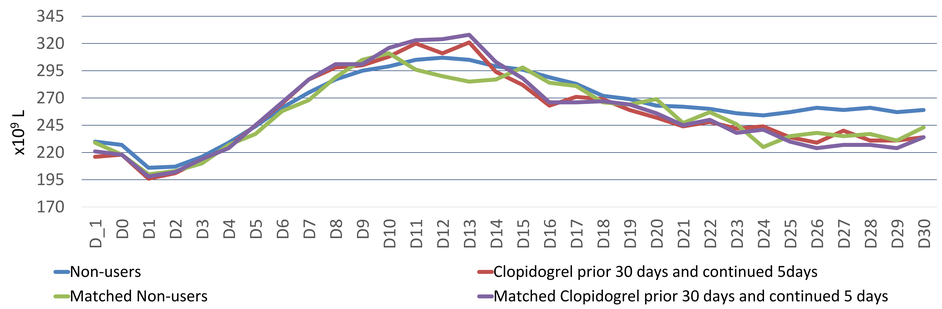
RESULTS

Outcomes	No. of events/No. of patients (%)		HR (95% CI)
	P2Y12 users	Non-users	
Inpatient mortality	12/288 (4.2)	20/288 (6.9)	**0.20 (0.04 – 0.91)**
30-day mortality	27/288 (9.4)	33/288 (11.5)	0.84 (0.50 - 1.41)
30-day readmission	72/276 (26.1)	67/268 (25.0)	1.05 (0.73 – 1.51)
30-day *S. aureus* reinfection	4/276 (1.5)	5/268 (1.9)	0.60 (0.14 – 2.51)
Microbiological eradication[1]	275/277 (99.3)	255/262 (97.3)	1.11 (0.89-1.40)
Thrombocytopenia[2]	82/250 (32.8)	81/229 (35.4)	0.98 (0.68-1.41)

HR=hazard ratio; CI=confidence interval. Bolded indicates p-value <0.05. Propensity score matched within a 0.001 caliper range. [1] Microbiological eradication was defined as a negative follow-up blood culture. Only includes patients with follow-up blood cultures. [2] Thrombocytopenia defined as a follow-up platelet count <150,000/uL. Only includes patients with follow-up platelet counts.

Figure 1. Mean follow-up platelet counts during admission, by day



RESULTS

In subgroup analyses, including baseline platelet count ≥100,000/uL, MRSA, MSSA, and narrow spectrum cephalosporins (cefazolin, cefotetan, cefoxitin, cefuroxime), only one significant difference was observed. Among those treated with narrow spectrum cephalosporins, time to microbiological eradication was higher in the clopidogrel group (HR 1.5, 95% CI 1.06-2.34). As utilization of other P2Y12 inhibitors remains low in the VA, we could not assess their impact on clinical outcomes.

CONCLUSIONS

Among patients receiving clopidogrel prior to a *S. aureus* bacteremia hospital admission and continuing clopidogrel for a minimum of 5 days, we observed a significant survival benefit compared with non-users. There is mounting evidence of anti-platelets either protecting against development of infections or improving clinical outcomes in those who develop infections, however the optimal timing of anti-platelet exposure requires further study.

ID Week 2020, October 21st -25th 2020, Virtual Event