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COMMENTARY

Antiplatelet Therapy in *Staphylococcus aureus* Bacteremia: No Time Like the Past?

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ABSTRACT In this invited commentary, we reflect on the accompanying study by A. R. Caffrey, H. J. Appaneal, K. L. LaPlante, V. V. Lopes, et al. (Antimicrob Agents Chemother 66:e02117-21, 2022, https://doi.org/10.1128/aac.02117-21), which analyzed the impact of clopidogrel use on clinical outcomes in *Staphylococcus aureus* bacteremia.

KEYWORDS *Staphylococcus aureus*, bacteremia, clopidogrel

Staphylococcus aureus bacteremia (SAB) causes considerable morbidity and mortality, with nearly 120,000 cases and 20,000 associated deaths occurring in the United States in 2017 alone (1). In the quest to find better treatments, ideas for novel or repurposed adjunctive therapies can come from unexpected sources, including studies for coronary artery disease. A *post hoc* analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial for acute coronary syndrome (ACS) showed that patients receiving the platelet ADP P2Y12 (P2Y12) inhibitor ticagrelor had a lower risk of infection-related death than those receiving clopidogrel (2, 3). Ticagrelor was subsequently shown to have *in vitro* bactericidal activity against Gram-positive organisms, including *S. aureus*, in addition to enhancing bactericidal activity of traditional antibiotics against *S. aureus* (4). Proposed mechanisms of action of this effect include enhancing platelet-mediated killing of *S. aureus* and reducing *S. aureus* toxin-mediated thrombocytopenia (5). This benefit of P2Y12 inhibitors did not appear to extend to clopidogrel in two recent retrospective clinical studies of patients receiving dual antiplatelet therapy (DAPT) with aspirin and either ticagrelor or clopidogrel after ACS, in which patients receiving DAPT that included ticagrelor had lower risk of infection than those being treated with clopidogrel (6, 7) (Table 1).

There is an analogous body of literature addressing antiplatelet therapy in infective endocarditis (IE). Platelet activation is critical for vegetation formation, and animal models have shown a protective effect of antiplatelet therapy against IE (8). Among patients with long-term use of antiplatelet therapy for noninfectious indications who subsequently developed endocarditis, embolic events were less common than among patients not on antiplatelet therapy in one cohort (9) but not a subsequent cohort that employed propensity matching (10). Additionally, a small (n = 115) randomized placebo-controlled trial (RCT) studying aspirin use in patients with infective endocarditis did not show reduced embolic events, and the patients may have increased bleeding (11). These studies demonstrate that the role of antiplatelet therapy, including clopidogrel, in the treatment of Gram-positive bacteremia is unsettled, and there is significant value in assessing this in a robust retrospective cohort.

In this issue of *Antimicrobial Agents and Chemotherapy*, Caffrey et al. report the results of a large (n = 11,499) retrospective, propensity-matched-cohort study that utilized national Veterans Affairs (VA) databases to assess the impact of clopidogrel use on clinical outcomes in patients admitted to VA hospitals in the United States from 2010 to 2018 with SAB (12). In addition to all-cause mortality, they evaluated important SAB-related outcomes, including 30-day *S. aureus* reinfection, time to microbiological clearance, and thrombocytopenia.

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TABLE 1 Selected clinical studies of antiplatelet therapy and infections[a]

Study	Study design	Comparison	Outcome
Infective endocarditis			
Chan et al. (11)	Randomized controlled trial	Aspirin ($n = 60$) vs placebo ($n = 55$) in patients with IE	No difference in embolic events (OR, 1.62; 95% CI, 0.68–3.86)
Anavekar et al. (9)	Single-center retrospective cohort	Chronic antiplatelet therapy[b] ($n = 125$) vs none ($n = 475$) in patients with IE	Fewer embolic events in patients on chronic antiplatelet therapy (aOR, 0.36; 95% CI, 0.19–0.68)
Pepin et al. (14)	Single-center retrospective cohort	Chronic antiplatelet therapy[c] ($n = 75$) vs none ($n = 166$) in patients with IE	Lower mortality in patients on chronic antiplatelet therapy (aOR, 0.27; 95% CI, 0.11–0.64)
Anavekar et al. (10)	Single-center retrospective cohort, propensity score matched	Chronic antiplatelet therapy[b] ($n = 116$) vs none ($n = 167$) in patients with IE	No difference in embolic events (aOR, 0.71; 95% CI, 0.37–1.36)
Pathickal et al. (15)	Single-center retrospective cohort	Chronic anticoagulant/antiplatelet therapy[d] ($n = 20$) vs no anticoagulant/antiplatelet therapy ($n = 14$) in patients with IE	Trend to more embolic events in patients with IE on anticoagulant/antiplatelet therapy (30% vs 7.1% [$P = 0.20$])
Infections in cardiovascular studies			
Storey et al. (3)	Retrospective cohort	Ticagrelor ($n = 9,235$) vs clopidogrel ($n = 9,186$) for DAPT after ACS	Fewer deaths due to sepsis in patients on ticagrelor (7 vs 23 [$P = 0.003$])
Lupu et al. (6)	Single-center retrospective cohort, propensity score matched	Ticagrelor ($n = 2,035$) vs clopidogrel ($n = 1,874$) for DAPT after ACS	Fewer Gram-positive infections with ticagrelor (aHR, 0.36; 95% CI, 0.21–0.61)
Butt et al. (7)	Nationwide retrospective cohort	Ticagrelor ($n = 20,073$) vs clopidogrel ($n = 6,533$) after PCI	Lower risk of SAB with ticagrelor (ARD, −0.19%; 95% CI, −0.32% to −0.05%)
Lee et al. (16)	Population-based cohort, propensity score matched	Ticagrelor ($n = 4,759$) vs clopidogrel ($n = 4,759$) after admission for MI	Fewer infectious events in patients on ticagrelor (aHR, 0.74; 95% CI, 0.64–0.85)

[a]ACS, acute coronary syndrome; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ARD, absolute risk difference; CI, confidence interval; DAPT, dual antiplatelet therapy; IE, infective endocarditis; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.
[b]Antiplatelet therapy included aspirin, dipyridamole, clopidogrel, ticlopidine, or any combination of agents.
[c]Antiplatelet therapy included aspirin, clopidogrel, or a combination of both.
[d]Anticoagulant/antiplatelet therapy included aspirin, clopidogrel, warfarin, apixaban, dabigatran, rivaroxaban, or any combination of agents.

In their final cohort, 87.6% of patients who were taking clopidogrel had a cardiovascular or cerebrovascular indication for P2Y12 inhibitor therapy, and 41.7% of patients who were not on treatment with a P2Y12 inhibitor had an indication for therapy. In their matched model, the authors found that inpatient and 30-day all-cause mortality was significantly lower among patients admitted with SAB who were prescribed clopidogrel for at least 30 days prior to admission and then continued clopidogrel treatment for at least 5 days after admission (hazard ratio [HR], 0.11; 95% confidence interval [CI], 0.01 to 0.86) than among patients who were not exposed to P2Y12 inhibitors within the previous year (HR, 0.43; 95% CI, 0.19 to 0.98). However, the authors did not find a statistically significant difference in other SAB-related outcomes.

This study is the largest retrospective analysis of clopidogrel use in patients with SAB. The authors used a thoughtfully designed propensity score matching to mitigate confounding. The resulting cohort was well balanced with respect to nearly all the anticipated confounders. The authors used important clinical variables to assess SAB-related outcomes. This allows us to gain insight into whether the differences between the groups were due to the potential direct antibacterial effect of clopidogrel or to other mechanisms. Interestingly, these SAB-related outcomes, such as time to clearance of bacteremia, did not differ between the groups. This suggests that some of the mortality difference may be attributable to noninfectious consequences of their illnesses, such as thrombosis and/or cardiovascular events, from which the patients treated with clopidogrel were relatively

protected. That is, appropriate management of underlying cardiovascular comorbidities may prevent progression from infection to prothrombotic inflammation to fatal vascular events.

Although the authors' well-balanced propensity-matched cohort allowed for minimization of confounding variables, residual confounding, including by indication, remains a potentially critical limitation of any study utilizing this method. Ideally, propensity matching aims to balance all possible factors responsible for a patient's treatment allocation, effectively isolating the treatment itself as the sole difference between groups. In reality, this is difficult to achieve when clinical judgment, access to care, or additional unaccounted traits influence treatment decisions. One of the limitations of this study hinges on the comparison between clopidogrel use and P2Y12 inhibitor nonuse among subjects for whom antiplatelet therapy was indicated. It is likely that subjects for whom a P2Y12 inhibitor was indicated but were not receiving therapy differed substantively from those on appropriate therapy, even if not captured in directly measured covariates. It would even be expected that patients with inadequately managed cardiovascular comorbidities at baseline will have worse outcomes, particularly with respect to overall mortality, regardless of their reason for hospital admission. It is similarly difficult to conclude that the observed difference in overall mortality can be solely or directly related to SAB, given that SAB-related outcomes were not different between groups. The authors carefully assessed for and did not find differences in microbiologic clearance and 30-day reinfection rates. Additionally, it may be difficult to extrapolate results to the broader population since the study was limited to a predominantly white, male, veteran population.

Despite the limitations inherent to any observational study, the authors have provided us with significant insight into the impact of long-term clopidogrel use on outcomes with SAB. What clinicians managing patients with SAB will want to know, however, is whether they should start P2Y12 inhibitor therapy for patients presenting with SAB, independent of a preexisting indication for antiplatelet therapy. As antiplatelet therapy was shown to be harmful in the only RCT that tested this strategy during an acute infection, the current answer is no (11). What, then, about long-term antiplatelet therapy for the prevention of infection-related mortality? Here, we must weigh the potential risks against the expected benefit. A network meta-analysis of P2Y12 inhibitor RCTs showed that approximately 5% of all patients receiving therapy experienced major bleeding events during the study periods (13). Consequently, before calling for an RCT to assess the role of long-term P2Y12 inhibition in SAB, we must first consider whether there is clinical equipoise to justify this risk of initiating P2Y12 inhibitors in patients without any other current indication for antiplatelet therapy. At this time, with the known risks of antiplatelet therapy, we would not advocate for a trial of prophylactic P2Y12 inhibitor therapy in patients without any other indication for their use. In contrast, among patients with an indication for P2Y12 inhibitor therapy who are at higher risk for SAB, such as patients receiving hemodialysis or with long-term central venous access, we would welcome additional evaluation of ticagrelor, as it has more *in vitro* and clinical evidence of benefit than does clopidogrel.

The authors leave us with a better understanding that patients with an indication for P2Y12 inhibitor therapy who receive treatment will have better outcomes with SAB than those who do not. This further reinforces the importance of cardiovascular risk stratification and appropriate management in patients with underlying cardiovascular disease: past performance in chronic disease management predicts future results with acute infections. This study also highlights the critical gap in our understanding the role of antiplatelet therapy in SAB and suggests that clinical trialists should systematically collect SAB-related outcomes in antiplatelet trials and cardiovascular outcomes in SAB trials. In the complex interplay between infection, thrombosis, and bleeding, there is still much to be learned.

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