Prehospitalization Antiplatelet Therapy Is Associated With a Reduced Incidence of Acute Lung Injury

A Population-Based Cohort Study

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Background: Acute lung injury (ALI) is a potentially fatal lung disease with few treatment options. Platelet activation is a key component of ALI pathophysiology and may provide an opportunity for prevention strategies. We examined the association of prehospitalization antiplatelet therapy with development of ALI in critically ill patients.

Methods: All Olmsted County, Minnesota, residents with a medical ICU admission in the year 2006 were evaluated. Patients with at least one major risk factor for ALI who did not meet criteria for ALI at the time of hospital admission were included in the analysis. Baseline characteristics, major risk factors for ALI, the presence of antiplatelet therapy at the time of hospitalization, and the propensity to receive this therapy were determined. The primary outcome was ALI or ARDS during the hospitalization. Secondary outcomes were ICU and hospital-free days and ICU and hospital mortality.

Results: A total of 161 patients were evaluated. Seventy-nine (49%) were receiving antiplatelet therapy at hospital admission; 33 (21%) developed ALI/ARDS. Antiplatelet therapy was associated with a reduced incidence of ALI/ARDS (12.7% vs 28.0%; OR, 0.37; 95% CI, 0.16-0.84; $P = .02$). This association remained significant after adjusting for confounding variables.

Conclusions: Prehospitalization antiplatelet therapy was associated with a reduced incidence of ALI/ARDS. If confirmed in a more diverse patient population, these results would support the use of antiplatelet agents in an ALI prevention trial.

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Abbreviations: ADP = adenosine diphosphate; ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; ASA = aspirin; CAD = coronary artery disease; CVD = cerebrovascular disease; LIPS = Lung Injury Prediction Score

ARDS and the less-severe acute lung injury (ALI) are devastating conditions that place heavy burdens on public health resources.^{1,2} Although the avoidance of progressive lung injury with lung-protective venti-

latory strategies have improved survival in patients with these conditions,³ additional effective therapeutic options in established ALI are lacking. With limited treatment options for established disease, prevention of ALI becomes increasingly important. Notably, preventive strategies for ALI and ARDS rarely have been studied, and effective prevention strategies currently are scarce.⁴

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ALI is a multifactorial disease where immune cell migration and activation within the lung ultimately result in injury to the alveolar-capillary membrane.⁵⁻⁹ This inflammatory process is complex and involves cells of diverse origin. Although best known for their primary role in hemostasis, accumulating evidence suggests an active role for platelets in both innate and adaptive immunity.¹⁰ Additionally, preclinical data have specifically identified a key role for platelets in ALI pathogenesis.¹¹ This association presents an obvious target for ALI prevention strategies.

Aspirin (ASA) and the adenosine diphosphate (ADP)-receptor antagonist clopidogrel bisulfate are commonly administered medications with multiple US Food and Drug Administration-labeled indications. Their ability to prevent platelet aggregation, through inactivation of cyclooxygenase with resultant reduction in thromboxane A₂ synthesis (eg, ASA), and blockade of ADP receptors on the platelet cell surface (eg, clopidogrel bisulfate, ticlopidine hydrochloride) has had a dramatic impact on cardiovascular health. Importantly, preclinical data suggest that these antiplatelet activities also may play a role in the prevention of ALI.^{12,13}

We hypothesized that patients receiving antiplatelet therapy would have a lower incidence of ALI/ARDS. To our knowledge, clinical investigations have not previously examined this potential association. The objective of this study was to evaluate the association between prehospitalization antiplatelet therapy and development of ALI/ARDS in a population-based cohort of ICU patients at high risk for ALI.

MATERIALS AND METHODS

Study Population

This population-based historical cohort study was undertaken with the approval of the institutional review board of the Mayo Clinic (Rochester, Minnesota). The study population included all Olmsted County, Minnesota, adult residents aged ≥ 18 years who required admission to an adult ICU in Rochester during the year 2006. We chose to restrict the study population to Olmsted County residents because it provides the opportunity for a population-based cohort. This design greatly reduces referral and lead-time bias, improving external validity and overall generalizability. Furthermore, in contrast to the local population, referral populations often present with established ALI/ARDS, precluding efforts to investigate preventive strategies.

The demographics of Olmsted County residents are typical of a suburban community in the Midwestern United States. The population consists largely of middle-class whites, with minorities representing 13% of the population according to 2006 US census reports. Because of its geographic isolation, critical care services are provided exclusively by two Mayo Clinic hospitals in Rochester. Inclusion criteria were the presence of at least one major risk factor for ALI and age > 18 years. Variables considered major risk factors for ALI were high-risk trauma, aspiration, sepsis, shock, pneumonia, and pancreatitis. Risk factors had to be present at the

time of hospital admission to be considered. Standardized definitions were used to identify these risk factors (high-risk trauma,^{14,15} aspiration,^{14,16} sepsis,^{17,18} shock,^{17,19} pneumonia,^{14,17} and pancreatitis^{17,20}). Cardiogenic shock was not included as a major risk factor for ALI and was not sufficient for inclusion in this study. Patients were excluded if they presented with ALI, had a previous ICU admission in the year 2006, or denied the use of their medical record for research. Postoperative patients were excluded because of the frequent discontinuation of antiplatelet agents before surgery and the inability to reliably determine the presence or absence of antiplatelet therapy at the time of hospital admission.

Predictor Variables

The exposure of interest was antiplatelet therapy at the time of hospital admission. Antiplatelet therapy was defined as documentation of use or administration in the medical record of any ASA-containing medication, clopidogrel bisulfate, ticlopidine hydrochloride, cilostazol, dipyridole, anagrelide, or persantine at the time of hospital admission. In an effort to ensure completeness of exposure ascertainment, use or administration of an antiplatelet agent was determined with two independent methods. The initial technique entailed manual review of the medical record by a trained critical care investigator. Additionally, an automated electronic search technique used an institutional database query tool (database discovery and query builder) to perform an automated search of the medical record for the variables of interest. We have recently validated this technique as more sensitive and specific than manual chart review.

Additional predictor variables included age at time of hospital admission, sex, baseline Charlson Comorbidity Index score,²¹ Acute Physiology and Chronic Health Evaluation (APACHE) III score calculated 1 h after ICU admission, coronary artery disease (CAD), cerebrovascular disease (CVD), statin therapy at the time of hospitalization, and predicted risk of developing ALI. We elected to use the APACHE III score at 1 h after ICU admission rather than the traditional APACHE III score at 24 h following ICU admission due to the potential for cause-effect inversion with the latter. Predicted risk of ALI was determined using the Lung Injury Prediction Score (LIPS).²² This score weighs the following variables to calculate a predicted risk of developing ALI while in the hospital: high-risk trauma, high-risk surgery, aspiration, sepsis, shock, pneumonia, pancreatitis, alcohol abuse, smoking, hypoalbuminemia, tachypnea, $\text{FIO}_2 > 35\%$, chemotherapy, and diabetes mellitus. Standardized definitions were used to identify these variables (alcohol abuse,^{23,24} smoking,^{24,25} hypoalbuminemia,^{14,26} tachypnea,^{14,27} chemotherapy,^{27,28} diabetes mellitus^{14,29}). Manual review of the medical record by a trained critical care investigator was used to determine the presence of these variables of interest.

Outcome Variables

The primary outcome of interest was development of ALI or ARDS during the hospitalization. Standard American-European Consensus Conference³⁰ criteria were used for determination of ALI/ARDS. Patients with possible ALI/ARDS were first identified with an electronic alert system (ALI sniffer) that uses a Microsoft standard query language-based integrative database, ICU datamart, where data are populated within 1 h of entry into the electronic medical record. An automatic alert was created if a patient had both the qualifying $\text{PaO}_2/\text{FIO}_2$ ratio on arterial blood gas analysis and a qualifying chest radiograph report (trigger words were "bilateral infiltrate" or "edema"). This system has been validated and has excellent negative predictive value for identifying ALI/ARDS.³¹ The records of identified patients were independently reviewed by two trained intensivist investigators

who underwent a structured ALI/ARDS tutorial prior to reviewing the electronic medical record. Secondary outcome measures were ICU and hospital mortality, ICU-free days at day 28 following ICU admission, and hospital-free days at day 60 following hospital admission.

Statistical Analysis

Dichotomous variables are presented as counts with percentages. Continuous data are presented as mean $\pm$ SD when normally distributed or median with 25% to 75% interquartile range when nonparametric. For univariate analyses, comparisons between the two groups were performed with a Pearson χ^2 test or Fisher exact test as appropriate for categorical variables. Continuous variables were tested with *t* test for parametric data or the Mann-Whitney *U* rank-sum test when nonnormally distributed. In an effort to better define the association between antiplatelet therapy and lung injury, a sensitivity analysis was performed evaluating the relationship between antiplatelet therapy and ARDS alone (ALI cases excluded). A second sensitivity analysis was performed to more specifically characterize the association between prehospitalization ASA therapy and ALI/ARDS.

Because observational studies risk unequal distributions of important covariates between treatment groups, the probability of receiving antiplatelet therapy was calculated with propensity scores. Covariates were entered into the model when significant differences ($P < .1$) were noted between antiplatelet user and nonuser baseline characteristics or when strong biologic associations were thought possible. The initial variables were age, sex, smoking, alcohol abuse, CAD, peripheral vascular disease, congestive heart failure, CVD, diabetes mellitus, obesity, and prehospitalization statin therapy. The model was refined with forward then backward stepwise regression, taking into account collinearity and interaction. The model was completed with nominal logistic regression. To control for pertinent confounders of the association between antiplatelet therapy and ALI/ARDS, we evaluated this association with multivariable adjustment using a Cox proportional hazards model. Covariates entered in this model included the APACHE III score, baseline risk for developing ALI (assessed with the LIPS), antiplatelet therapy, and the propensity for receiving antiplatelet therapy. Time zero was defined as the time and date of hospital admission. Patients who remained free of ALI/ARDS were censored at death, date of hospital discharge, or administratively at 28 days following hospitalization.

RESULTS

A total of 161 patients met the inclusion criteria for this investigation. The flow of patient evaluation, exclusion, and enrollment are shown in Figure 1. Seventy-nine (49%) of these patients were receiving antiplatelet therapy at the time of hospitalization. Sixty-eight were taking an ASA-containing medication alone, three were receiving clopidogrel bisulfate alone, and one was receiving the antiplatelet agent anagrelide. Seven patients were being treated with both ASA and clopidogrel bisulfate. Demographic and baseline information are presented in Table 1. Patients taking antiplatelet agents were older; had a higher Charlson Comorbidity Index and APACHE III 1-h score; and had a greater frequency of smoking, CAD, CVD, and prehospitalization statin ther-

FIGURE 1. Study population flow. ALI = acute lung injury.

apy. Most patients presented with more than one ALI risk factor or modifier, but the overall predicted risk of ALI/ARDS as assessed by the LIPS was the same for both groups (median score, 3; 95% CI, 1.5-4.0). With the exception of a greater frequency of smoking in those taking antiplatelet medications, the frequency of specific ALI risk factors were similar between the two groups (Table 1). The primary ICU admission category was similar among the exposed and nonexposed patients as well.

A total of 33 patients developed ALI/ARDS; 24 of these met criteria for ARDS. Univariate analyses evaluating patient outcome by the presence of antiplatelet therapy are shown in Table 2. Patients receiving antiplatelet therapy had a lower incidence of ALI/ARDS (12.7% vs 28.0%; unadjusted OR, 0.37; 95% CI, 0.16-0.84; $P = .02$) compared with those not receiving an antiplatelet agent. The median time from hospital admission to American-European Consensus Conference criteria for ALI/ARDS was 1.8 days (interquartile range, 1 to 3.7). Three patients developed ALI/ARDS > 7 days after hospital admission. None of these patients were receiving antiplatelet therapy prior to hospitalization, and none received an antiplatelet medication prior to ALI/ARDS onset.

Although statistical significance was lost when a sensitivity analysis was performed, restricting the outcome to patients who developed ARDS (excluding

Table 1—Demographics and Baseline Characteristics

Parameter	Antiplatelet Agents (n = 79)	No Antiplatelet Agents (n = 82)	P Value
Age	77 ± 12	66 ± 19	< .01
Female sex	37 (46.8)	38 (46.3)	.95
Primary ICU admission category			
Neurologic	4 (5.1)	4 (4.9)	.59
Cardiovascular	2 (2.5)	3 (3.7)	...
Respiratory	35 (44.3)	27 (32.9)	...
GI	5 (6.3)	5 (6.1)	...
Sepsis	19 (24.1)	23 (28.1)	...
Trauma	8 (10.1)	16 (19.5)	...
Other	6 (7.6)	4 (4.9)	...
Charlson Comorbidity Index score	6 (5-8)	4 (3-6)	< .01
APACHE III at ICU hour 1	46 (34-57)	39 (27-54)	.03
LIPS	3 (1.5-4)	3 (1.5-4)	.71
Risk factors for ALI at the time of hospital admission			
Aspiration	11 (13.9)	8 (9.8)	.41
Pancreatitis	2 (2.5)	2 (2.4)	1
Pneumonia	30 (38.0)	25 (30.5)	.32
Sepsis	19 (24.1)	25 (30.5)	.36
Positive shock index	40 (50.6)	47 (57.3)	.39
Trauma	4 (5.1)	4 (4.9)	1
Risk modifiers for ALI at the time of hospital admission			
Hypoalbuminemia (n = 43)	4 (5.1)	6 (7.3)	.55
Chemotherapy	1 (1.3)	1 (1.2)	1
Diabetes mellitus	27 (34.2)	17 (20.7)	.06
Smoking	46 (58.2)	33 (40.2)	.02
Alcohol abuse	3 (3.8)	9 (11.0)	.08
Tachypnea (RR > 30)	22 (27.9)	17 (20.7)	.29
FIO ₂	0.32 (0.21-0.50)	0.29 (0.21-0.6)	.89
Coronary artery disease	44 (55.7)	10 (12.2)	< .01
Cerebrovascular disease	11 (13.9)	4 (4.9)	.05
Congestive heart failure	18 (22.8)	10 (12.2)	.08
BMI	26.0 (22.2-30.0)	25.2 (22.0-31.0)	.69
Prehospital statin therapy	39 (49.4)	9 (11.0)	< .01
Mean arterial pressure	66 (53-81)	71 (59-88)	.1
Admission PaO ₂ /FIO ₂ (n = 78)	182 (146-252)	199 (98-244)	.65
Mechanical ventilation on ICU admission	8 (10.1)	11 (13.4)	.52
DNR status on ICU Admission			
Full code	60 (76.9)	69 (84.2)	.2
DNR/DNI	13 (16.7)	12 (14.6)	...
DNR	5 (6.4)	1 (1.2)	...

Data are presented as mean ± SD, No. (%), or median (interquartile range). ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; DNI = do not intubate; DNR = do not resuscitate; LIPS = Lung Injury Prediction Score; RR = respiratory rate.

patients only meeting criteria for ALI [n = 24]), the effect size was similar (OR, 0.43; 95% CI, 0.17-1.07; *P* = .06). The subgroup analysis, including patients who received prehospitalization ASA therapy

alone (clopidogrel bisulfate, anagrelide, and combined ASA/clopidogrel bisulfate therapy excluded), noted a similar reduction in the incidence of ALI/ARDS when compared with those who received no form of

Table 2—Univariate Analysis of Patient Outcomes by the Presence of Antiplatelet Therapy on Admission to the Hospital

Outcome	Antiplatelet Therapy (n = 79)	No Antiplatelet Therapy (n = 82)	P Value
ALI/ARDS	10 (12.7)	23 (28.1)	.02
ICU mortality	9 (11.4)	9 (11.0)	.93
Hospital mortality	10 (12.7)	13 (15.9)	.56
ICU-free days ^a	25.9 (21.6-27.0)	25.6 (19.7-27.0)	.55
Hospital-free days ^b	52.8 (34.9-55.8)	51.8 (32.1-56.2)	.80

Data are presented as No. (%) or median (25% to 75% interquartile range). See Table 1 legend for expansion of abbreviation.

^aDetermined at ICU day 28.

^bDetermined at 60 days following hospital admission.

prehospitalization antiplatelet therapy (13% vs 28%; OR, 0.39; 95% CI, 0.17-0.92; $P = .03$). No statistically significant differences were noted in ICU or hospital mortality, ICU-free days at day 28 following ICU admission, or hospital-free days at day 60 following admission to the hospital (Table 2).

Multivariable evaluation of the association between antiplatelet therapy and development of ALI/ARDS with adjustment for the propensity to receive antiplatelet therapy was performed as outlined previously. The final propensity model included age, sex, CAD, diabetes mellitus, smoking, and prehospitalization statin therapy. CHF and CVD were not statistically significant predictors of antiplatelet therapy and were not included in the final propensity model. Peripheral vascular disease was removed from the model because of evidence of collinearity with CAD. The final model performed well with an area under the receiver operating characteristic curve of 0.84. After adjustment for baseline severity of illness at the time of ICU admission (APACHE III score), propensity for receiving antiplatelet therapy, and baseline risk for developing ALI (assessed with the LIPS), antiplatelet therapy remained a significant protective factor with a risk ratio of 0.34 (95% CI, 0.13-0.88; $P = .03$) (Table 3).

DISCUSSION

In the present study, we conducted a retrospective cohort evaluation of the effect of prehospitalization antiplatelet therapy on the development and severity of ALI/ARDS in a nonsurgical ICU population. The major conclusion of this study is that patients who were taking antiplatelet medications at the time of hospital admission had a lower incidence of ALI/ARDS compared with patients who were not taking antiplatelet medications. These benefits were apparent despite the fact that the patients receiving antiplatelet medications were older, had more advanced disease, and had greater severity of illness at the time of ICU admission.

Table 3—Cox Proportional Hazard Analysis for Event-Free Survival Through 28 d From Hospital Admission

Parameter	Risk Ratio	95% CI	P Value
Antiplatelet therapy	0.34	0.13-0.88	.03
Propensity for antiplatelet therapy ^a	1.08	0.93-1.26	.32
APACHE III at ICU hour 1	1.02	1.00-1.04	.08
LIPS	1.67	1.33-2.12	< .01

See Table 1 legend for expansion of abbreviations.

^aThe propensity for antiplatelet therapy was calculated based on a multivariate logistic regression analysis that included age, sex, coronary artery disease, diabetes mellitus, smoking, and prehospitalization statin therapy.

The association between antiplatelet therapy and prevention of ALI/ARDS was robust and remained significant with multivariate adjustment. This adjustment included multiple pertinent baseline variables associated with risk for ALI as well as the propensity for receiving antiplatelet therapy. Although statistical significance was lost in the sensitivity analysis specifically evaluating the association of antiplatelet therapy with ARDS (ALI cases excluded), the effect estimate was similar to the primary analysis. This lack of statistical significance likely relates to the loss of power in this restricted analysis. We did not find convincing evidence for an effect on ICU or hospital mortality or ICU- or hospital-free days.

To our knowledge, this clinical investigation is the first to demonstrate the protective effects of platelet inhibition in patients at risk for ALI. Importantly, platelet activation has been linked to numerous biologic processes beyond hemostasis. Examples include inflammatory reactions, vascular permeability, and altered immune function.^{32,33} Recent clinical evidence also suggests a potential for the prevention of organ dysfunction when antiplatelet therapy is taken before an event that causes hospitalization and ICU treatment.³⁴ Moreover, preclinical studies suggest that platelet activation and sequestration play a central role in the pathogenesis of ALI/ARDS.^{11,35-37}

Once activated by thrombin, ADP, platelet-activating factor, and/or thromboxane A₂, platelets adhere to the vascular endothelium within the lungs, aggregate, and interact with polymorphonuclear cells through platelet P-selectin, glycoprotein IIb/IIIa, and von Willebrand Factor.³⁷ This process is termed “secondary capture” and has been shown to increase pulmonary vascular permeability.³⁵ The resultant escape of fluid and plasma proteins from the intravascular space into the lungs leads to the fully established syndromes of ALI and ARDS.^{5,9,30,37-40} In animal models, blockade of P-selectin has been shown to reduce neutrophil recruitment and to have a protective effect in acid-induced ALI.³⁷ Furthermore, in a two-hit model of transfusion-related ALI, Looney and colleagues¹¹ recently noted evidence for lung protection with both preinjury platelet depletion and pretreatment with ASA.

In light of recent conflicting evidence associating statin therapy with improved ALI outcomes⁴¹⁻⁴³ and the frequent coadministration of statin drugs with antiplatelet agents, we evaluated the impact of statin therapy on the development of ALI as well as its interaction with the primary association of interest: antiplatelet therapy and ALI/ARDS. Notably, the frequency of statin use was substantially higher in patients receiving antiplatelet therapy than in those not receiving antiplatelet medications (49.4% vs 11.0%; $P < .01$). However, univariate analysis did not

find a significant association between statin therapy and development of ALI/ARDS (statin, 16.7%; no statin 22.1%; $P = .43$). Inclusion of statin therapy in the Cox proportional hazards model evaluating the association between antiplatelet therapy and ALI/ARDS did not significantly affect the test results (risk ratio for antiplatelet therapy and development of ALI/ARDS, 0.27; 95% CI, 0.09-0.79; $P = .01$). Statin therapy was not associated with ALI/ARDS in this model.

Our study has a number of important limitations. The first is its retrospective, observational nature, with the inherent potential for bias and confounding. For example, we are unable to comment on the duration of prehospitalization antiplatelet therapy; rather, we were only able to determine the presence or absence of antiplatelet therapy at the time of hospital admission. Although efforts were made to adjust for both baseline differences in risk for ALI and propensity to receive antiplatelet therapy, there nonetheless is potential for additional unmeasured confounding effects. A second limitation is our restriction to medical ICU patients. Surgical patients were excluded because of our inability to determine whether antiplatelet therapy was either continued or discontinued. As a result, our findings cannot be generalized to surgical populations, particularly in light of their increased risk of bleeding. Additional subgroup analyses and investigations of interaction effects also were limited by our sample size.

A third concern with this evaluation is the possibility that improved outcomes in the antiplatelet cohort were actually a marker of better overall health-care maintenance rather than evidence of a true protective effect. Although difficult to control directly, the relative ease of access to health care in this community and robust penetration of health-care services into the population studied mitigate the likelihood of this effect. Finally, perhaps the greatest limitation with this study is the single-center, tertiary-care nature of the institution providing care to the study population, which raises concern for both referral and institution-specific bias as well as for overall generalizability. We attempted to minimize referral bias and improve generalizability with a population-based study design approach. Nonetheless, unique aspects of the Olmsted County, Minnesota, population and the care provided at Mayo Clinic Rochester may limit our ability to generalize the study results. Recognizing the need to reproduce these findings, we are pursuing this association in a multicenter cohort.

In conclusion, in this population-based retrospective cohort evaluation of Olmsted County, Minnesota, residents requiring medical critical care services, prehospitalization antiplatelet therapy was associated with a reduced incidence of ALI/ARDS. In light of

our study results and the presence of strong biological plausibility, this association warrants further study in a more diverse patient population. If confirmed, a prospective evaluation of antiplatelet therapy as a preventive strategy in patients at risk for ALI could be considered.

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