Prehospital Aspirin Use Is Associated With Reduced Risk of Acute Respiratory Distress Syndrome in Critically Ill Patients: A Propensity-Adjusted Analysis*

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Objectives: Platelet activation plays an active role in the pathogenesis of acute respiratory distress syndrome. In our prior study of 575 patients at high risk for acute respiratory distress syndrome, concurrent statin and aspirin use was associated with reduced acute respiratory distress syndrome. However, the largest study (n = 3,855) to date found no significant benefit of prehospital aspirin in a lower-risk population when adjusted for the propensity for aspirin use. We aimed to determine whether prehospital aspirin use is associated with decreased acute respiratory distress syndrome in patients at high risk for acute respiratory distress syndrome after adjusting for the propensity to receive aspirin.

Design: Secondary analysis of patients enrolled prospectively in the Validating Acute Lung Injury Markers for Diagnosis study.

Patients: A total of 1,149 critically ill patients (≥ 40 years old) admitted to the medical or surgical ICUs of an academic tertiary care hospital including 575 previously reported patients as well as additional patients who were enrolled after completion of the prior statin and aspirin study.

Intervention: None.

Measurements and Results: Of 1,149 patients, 368 (32%) developed acute respiratory distress syndrome during the first 4 ICU days and 287 (25%) patients had prehospital aspirin use. Patients with prehospital aspirin had significantly lower prevalence of acute respiratory distress syndrome (27% vs 34%; $p = 0.034$). In a multivariable, propensity-adjusted analysis including age, gender, race, sepsis, and Acute Physiology and Chronic Health Evaluation score II, prehospital aspirin use was associated with a decreased risk of acute respiratory distress syndrome (odds ratio, 0.66; 95% CI, 0.46–0.94) in the entire cohort and in a subgroup of 725 patients with sepsis (odds ratio, 0.60; 95% CI, 0.41–0.90).

Conclusions: In this selected cohort of critically ill patients, prehospital aspirin use was independently associated with a decreased risk of acute respiratory distress syndrome even after adjusting for the propensity of prehospital aspirin use. These findings support the need for prospective clinical trials to determine whether aspirin may be beneficial for the prevention of clinical acute respiratory distress syndrome. (*Crit Care Med* 2015; 43:801–807)

Key Words: acute lung injury; acute respiratory distress syndrome; aspirin; sepsis

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Despite advances in critical care, the acute respiratory distress syndrome (ARDS) remains a life-threatening condition associated with a hospital mortality of 25–40% (1–3). Although numerous promising therapies have been effective in the prevention of ARDS in experimental models, successful translation to clinical application is still lacking (4–7).

Growing evidence suggests that platelets play a crucial role in the pathogenesis of ARDS. The possible mechanisms by which platelets contribute to ARDS include activation of endothelial cells by release of proinflammatory mediators (8–10) and adherence of platelets to lung capillary endothelial cells leading to activation of attached leukocytes (11). Preclinical studies have shown that the platelet inhibitor aspirin can prevent or treat ARDS by decreasing neutrophil activation, tumor necrosis factor-α expression in pulmonary intravascular macrophages, plasma thromboxane B2 levels, and platelet sequestration in the lungs (12–17).

In a multicenter clinical study, Harr et al (18) showed that prehospital antiplatelet therapy (predominantly aspirin) was associated with a decreased risk of lung dysfunction and multiple organ failure in patients with high-risk blunt trauma who received blood transfusions. Our group reported in a prior study of 575 patients in the Validating Acute Lung Injury Markers for Diagnosis (VALID) cohort that concurrent statin and aspirin use, but not aspirin alone, was associated with reduced risk of ARDS (19). However, this study was likely underpowered to show an independent association between prehospital aspirin use and reduced risk of ARDS, given the large proportion of patients who were receiving both prehospital statin and prehospital aspirin therapy. By contrast, the largest clinical study to date found no significant association of prehospital aspirin use and risk of ARDS when adjusted for a propensity score that quantified the propensity to receive aspirin therapy (20). However, the overall prevalence of ARDS in that study was low.

To further characterize the possible benefit of prehospital aspirin use in ARDS, we performed a new cross-sectional analysis of the entire prospectively collected VALID cohort with approximately 2,500 critically ill patients enrolled during a 6-year interval. This analysis included the previously studied 575 patients as well as patients who were enrolled in the VALID cohort after our previous study was published (19). The aim of the study was to investigate the association between prehospital aspirin therapy and development of ARDS in a heterogeneous group of critically ill patients at high risk for ARDS as well as in the subgroup of patients with sepsis, adjusting for propensity to receive aspirin.

MATERIALS AND METHODS

Description of the VALID Cohort

We studied patients who were prospectively enrolled from January 23, 2006 to February 18, 2012 in the VALID study. The VALID study was designed to identify and validate plasma biomarkers for diagnosis and prognosis of ARDS. The Vanderbilt University Institutional Review Board approved the study protocol, and written informed consent was obtained from the patient or their surrogate when possible. Because the study carries minimal risk to the study participants, the institutional review board also granted a waiver of informed consent.

Patients eligible for the VALID study were those 18 years old or older admitted to the medical, surgical, cardiovascular, and trauma ICUs who remained in the ICU for at least 2 days. Detailed exclusion criteria for patients in VALID were described previously (19). Clinical data, including demographics, prehospital medications, medical history, and admission diagnoses, were collected at admission; variables such as hemodynamics, ventilator variables, laboratory values, and in-hospital medications were collected daily during the first 4 days after enrollment. Prehospital medications including aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and clopidogrel were recorded. For prehospital medication use, the medical record was manually reviewed by the research coordinator for mention of the relevant medication (such as aspirin or an aspirin-containing medicine) in the admission history and physical(s), the list of prehospital medicines (routinely collected for all admitted patients), and any other physician or ancillary health personnel notes around the time of admission. This was done prospectively at the time when the patients were enrolled into the VALID study. For in-hospital medication use including aspirin use, manual review of the medical record was supplemented with query of the Vanderbilt electronic medication administration record for specific medications of interest including all doses of aspirin or aspirin-containing medicines received by the patient during the hospitalization of interest. The diagnoses of sepsis, organ dysfunction, and ARDS were made by study investigators in accordance with published consensus definitions (21–23). Acute lung injury (ALI) or ARDS during the first 5 days in hospital was defined by the American European Consensus Conference definitions. For ARDS ascertainment, two-physician review of chest radiographs and clinical data was done. When arterial blood gas data were not available for a given day, then the Sp_{O_2}/F_{IO_2} ratio was used to assess the level of hypoxemia (24). In keeping with the recent Berlin definition of ARDS (25), the diagnosis of ALI or ARDS is subsequently referred to as "ARDS herein." Outcome data, including duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, and hospital mortality, were collected.

Study Population

During the 6-year study period, 2,503 patients enrolled into the VALID study were considered for inclusion in the current study (**Fig. 1**). We excluded patients who transferred from other hospitals without thorough medical information and excluded patients with an ICU stay less than 48 hours. Patients admitted to the trauma ICU were excluded since overall this younger group of patients was less likely to be taking prehospital aspirin and preadmission medication histories were often not available. To avoid the confounding effects of cardiovascular diseases that might be associated with both higher rates of aspirin use and lower rates of ARDS, we excluded patients admitted to the cardiovascular ICU and patients with an acute cardiac diagnosis. We also excluded patients admitted for elective surgery because antiplatelet agents are frequently discontinued before surgery and medication history may be inaccurate. Finally, we excluded patients less than 40 years old because prehospital aspirin was rarely prescribed in that age group.

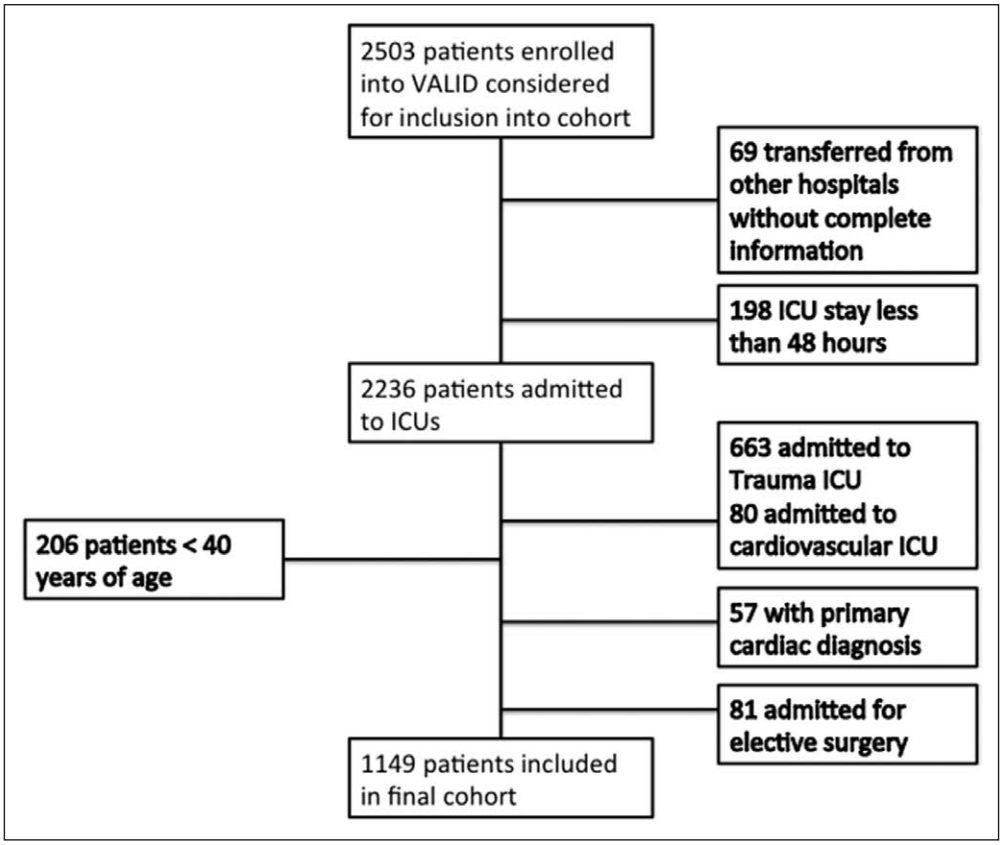

Figure 1. Study flow diagram. VALID = Validating Acute Lung Injury Markers for Diagnosis.

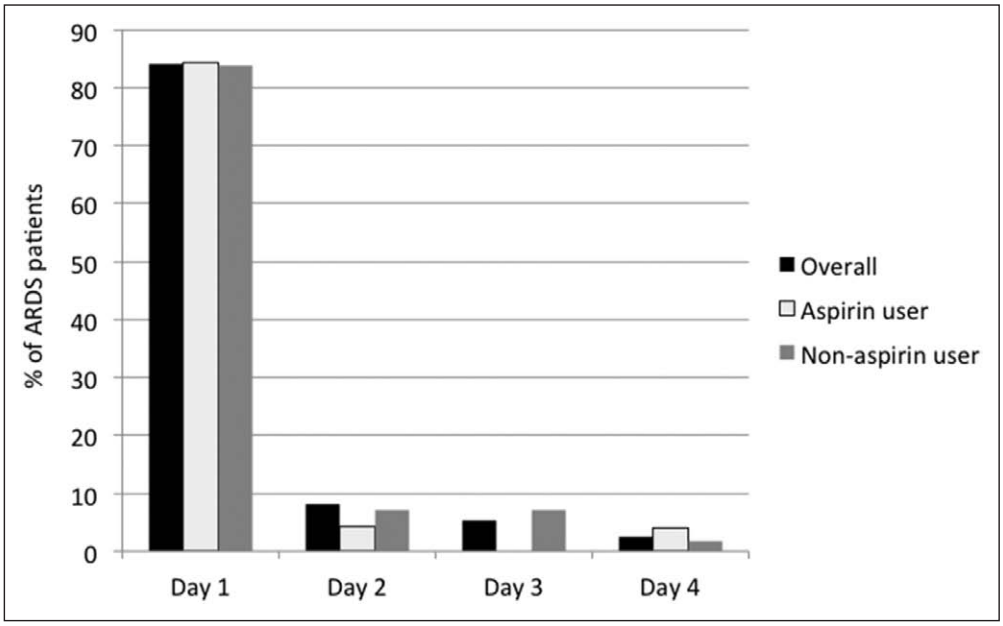

Figure 2. Timing of onset of acute respiratory distress syndrome (ARDS) during the first 4 days of ICU admission among the 368 patients in the cohort who developed ARDS. There were 309 patients who developed ARDS on day 1, 30 patients on day 2, 20 patients on day 3, and 9 patients on day 4.

Statistical Analysis

As the majority of continuous variables are not normally distributed, data are expressed as median values and interquartile range. Categorical variables are expressed as counts and percentage. Comparison of two groups with continuous variables was conducted using Wilcoxon rank-sum test. Comparison of categorical variables between two groups was performed with a chi-square test or Fisher exact test. A propensity score was created for the probability of receiving prehospital aspirin therapy. The a priori selected variables included in the propensity score model were age, hypertension, diabetes mellitus, chronic kidney disease, end-stage renal disease, peripheral vascular disease, congestive heart failure, coronary artery disease, cerebral vascular disease, and prehospital statin use. Propensity adjustment, rather than matching, was used to increase the power of our analysis and avoid misclassification of patients. We used the Hosmer and Lemeshow goodness-of-fit test to perform score diagnostics for the propensity score ($p = 0.27$) and for the ARDS regression model ($p = 0.33$). Multivariate logistic regression models with a priori selected variables were developed for diagnosis of ARDS and in-hospital mortality. IBM SPSS Statistics (version 21.0, Chicago, IL) was used for statistical analysis; a two-sided significance level of 0.05 was used for statistical inference.

RESULTS

A total of 1,149 VALID patients met the inclusion and exclusion criteria and were included in the current study (Fig. 1). Of these, 368 patients (32%) developed ARDS during the first 4 days of ICU admission. The majority of the patients who developed ARDS (84%) developed it on the first ICU day (**Fig. 2**). **Table 1** includes a comparison of baseline characteristics and clinical outcomes between patients with and without ARDS. Baseline demographic characteristics were not associated with development of ARDS. Patients with ARDS were significantly less likely to have a history of hypertension.

TABLE 1. Comparison of Demographic Data and Outcomes Between Patients With and Without Acute Respiratory Distress Syndrome

	ARDS (*n* = 368) (%)	Non-ARDS (*n* = 781) (%)	*p*
Age (yr)	59 (52–69)	61 (52–68)	0.801
Male	192 (52)	439 (53)	0.204
Caucasian	320 (87)	682 (87)	0.925
Current smoker	114 (31)	235 (30)	0.783
Diabetes	109 (30)	265 (34)	0.157
Hypertension	184 (50)	456 (58)	0.009
Chronic kidney disease	70 (19)	179 (22)	0.312
On dialysis	13 (3.5)	45 (5.8)	0.114
Prehospital aspirin	77 (21)	210 (27)	0.034
Acute Physiology and Chronic Health Evaluation II score	29 (24–34)	25 (20–31)	< 0.001
Length of ICU stay (d)	8 (5–14)	5 (3–9)	< 0.001
Time on ventilator (d)	5 (2–9)	2 (0–5)	< 0.001
Shock	224 (61)	341 (44)	< 0.001
Hospital stay (d)	15 (9–23)	11 (7–20)	< 0.001
Hospital mortality	119 (32)	129 (17)	< 0.001

ARDS = acute respiratory distress syndrome.
Data are median (interquartile range) or *n* (%) as indicated.

TABLE 2. Comparison of Demographic Data and Outcomes Between Patients With Prehospital Aspirin Use and Without Aspirin Use

	Aspirin Users (*n* = 287) (%)	Nonaspirin Users (*n* = 862) (%)	*p*
Age (yr)	67 (61–74)	58 (50–65)	0.801
Male	167 (58.2)	464 (53.8)	0.218
Caucasian	253 (88.2)	749 (86.9)	0.611
Current smoker	69 (24)	280 (32.5)	0.008
Diabetes	123 (42.9)	251 (29.1)	< 0.001
Hypertension	224 (78)	416 (48.3)	< 0.001
Chronic kidney disease	87 (30.3)	153 (17.7)	< 0.001
On dialysis	18 (6.3)	40 (4.6)	0.278
Chronic liver disease	7 (2.4)	127 (14.7)	< 0.001
Cerebral vascular disease	20 (7)	27 (3.1)	0.006
Peripheral vascular disease	45 (15.7)	57 (6.6)	< 0.001
Coronary artery disease	147 (51.2)	169 (19.6)	< 0.001
Congestive heart failure	67 (23.3)	104 (12.1)	< 0.001

Data are median (interquartile range) or *n* (%) as indicated.

Patients with ARDS also had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores at the time of ICU admission and had longer hospital and ICU length of stays.

Of the 1,149 enrolled patients, a total of 287 patients (25%) were receiving any aspirin-containing medication before hospitalization. Patients taking aspirin were more likely to have diabetes mellitus, hypertension, chronic kidney disease, cerebrovascular disease, peripheral vascular disease, coronary artery disease, and congestive heart failure (**Table 2**). In an unadjusted analysis, patients who took prehospital aspirin had a significantly lower rate of ARDS (27%) than that in patients not receiving prehospital aspirin therapy (33%; $p = 0.034$) (**Fig. 3**). By contrast, patients who took prehospital statins (29% vs 33%; $p = 0.158$) or ACE inhibitors (28% vs 33%; $p = 0.129$) did not have a significantly lower rate of ARDS than that in patients who did not take those medications. Patients who took both aspirin and statins had a lower prevalence of ARDS than the prevalence in patients who received neither (23% vs 34%; $p = 0.008$). Of the 287 patients with prehospital aspirin use, 92 patients (31%) were taking high-dose aspirin (325 mg/d) and 184 patients (64%) were taking low-dose aspirin (81 mg/d). In 11 patients, the dose was not available. The prevalence of ARDS did not differ significantly by aspirin dose (25% in the higher dose vs 27% in the lower dose; $p = 0.773$). Of 287 patients receiving prehospital aspirin, 150 patients (52.3%) continued to receive aspirin during the first 3 days of ICU stay; among these 150 patients, 11% ($n = 17$) received aspirin for 1 day, 18% ($n = 27$) received aspirin for 2 days, and 71% ($n = 106$) received aspirin for 3 days. Of 287 patients receiving prehospital aspirin, the prevalence of ARDS was not different between patients who discontinued aspirin use during hospitalization compared with patients who continued aspirin use (22% vs 31%; $p = 0.083$). Comparing the ARDS prevalence among prehospital aspirin users with in-hospital 1-, 2-, and 3-day aspirin use, there was no significant difference (29.4%, 37%, and 30.2%, respectively; $p = 0.284$).

To control the potential confounding associated with baseline differences in prehospital aspirin users and nonusers, we used a propensity score to adjust for propensity to receive aspirin in the prehospital setting. In a multivariate logistic regression model that included age, gender, race, sepsis, and APACHE II score along with the aspirin propensity score, prehospital aspirin use was significantly associated with a lower rate of ARDS (odds ratio [OR], 0.659; 95% CI, 0.46–0.94; $p = 0.023$) (**Table 3**).

Among the 1,149 patients, 725 patients (63%) were diagnosed with sepsis during the first 4 days of ICU admission. To determine whether prehospital aspirin use had a stronger association with a lower rate of ARDS in sepsis patients,

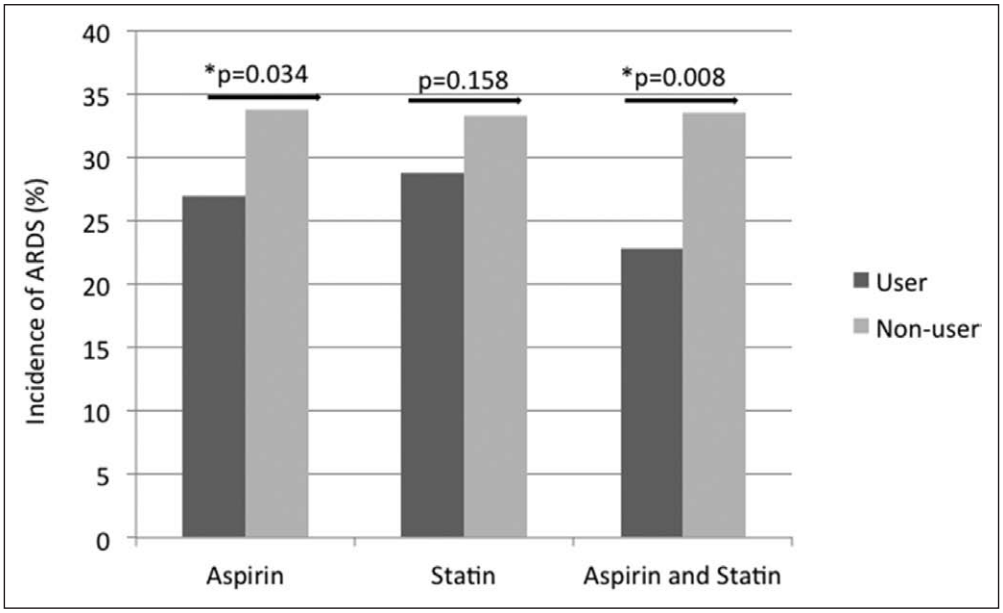

Figure 3. Prevalence of acute respiratory distress syndrome (ARDS) in patients with and without prehospital aspirin, statin, or combined aspirin and statin use.

we repeated the same regression models as above in the 725 patients with sepsis (**Table 4**). Prehospital aspirin use was significantly associated with a lower rate of ARDS in sepsis patients either adjusted by propensity score (OR, 0.62; 95% CI, 0.41–0.92; $p = 0.018$) or adjusted by propensity score and selected variables (OR, 0.61; 95% CI, 0.41–0.90: $p = 0.014$).

Of the 1,149 patients in the cohort, 248 patients (21.6%) died before discharge from the hospital. In a multivariate logistic regression model, first-day APACHE II score and presence of any sepsis, ARDS, or shock during the first 4 days of ICU admission were significantly associated with in-hospital mortality (**Table 5**). Prehospital aspirin use, adjusted by propensity score, had a trend toward association with lower in-hospital mortality that did not reach statistical significance (OR, 0.697; 95% CI, 0.47–1.03; $p = 0.075$).

DISCUSSION

In this expanded cohort, prehospital aspirin use was significantly associated with a lower prevalence of ARDS during the first 4 days of ICU stay even when controlling for potential confounding factors and adjusting for the propensity to receive aspirin. In addition, the association was even stronger in patients with sepsis. By contrast, prehospital statin use was not significantly associated with a lower prevalence of ARDS although the subgroup that received both aspirin and statins had the lowest overall prevalence of ARDS.

The finding that prehospital aspirin use is associated with a decreased risk of ARDS in critically ill patients is consistent with the known beneficial effects of aspirin in both clinical and experimental ALI (13, 26, 27). In addition, aspirin also has potent effects on treatment and prevention of sepsis via antiplatelet and anti-inflammatory effects in preclinical and clinical studies (28–30). This could, in part, explain why the association between prehospital aspirin use and ARDS is stronger in the sepsis subgroup in our study.

The current findings can be compared with that in prior studies of the association between prehospital aspirin use and ARDS. In the largest prior study, Kor et al (20) reported that there was no significant association between prehospital aspirin therapy and in-hospital development of ARDS after adjusting for the propensity to receive aspirin therapy. However, the patient population was substantially different compared with the current study, with a much lower overall prevalence of ARDS (240/3,855, 6.2%) due to inclusion of a large number of patients who were not critically ill. The smaller number of ARDS cases in that study may have limited the power to detect a significant association between aspirin use and risk of ARDS. Of note, the unadjusted OR (0.65) and propensity-adjusted OR (0.70) for development of ARDS in prehospital aspirin users in the study by Kor et al were almost identical to the current findings. Also of note, the study by Kor et al included 947 patients (24.5%) admitted with high-risk trauma. In our study, we excluded patients with severe traumatic injuries for two reasons. First, the trauma patients enrolled in VALID were predominantly young adults, and few of them had prehospital aspirin use. Second, most of the patients admitted to the trauma ICU were unconscious and had no surrogate immediately available, making the prehospital medication history unreliable. Given the very low likelihood of prehospital aspirin use in the trauma subgroup, inclusion of this group in the analysis might have obscured any aspirin-related signal.

In our prior analysis of a smaller group of patients enrolled in the VALID cohort (who were also part of the current study), we found a significant association between prehospital statin use or prehospital statin and aspirin use and lower risk of ARDS, but there was no significant association of aspirin alone with ARDS. There are several possible explanations for the different results in this larger group of patients from the VALID cohort. First, it is likely that the prior study was underpowered to detect an aspirin effect. Second, based on the current findings, it is possible that the prior association between statin use and reduced risk of ARDS was confounded by aspirin use, an effect that is only fully apparent in this larger cohort. Either way, the discordant results between our prior study and our current study underscore the need for prospective clinical trials to more definitively answer these questions. Discouragingly, a large National Institutes of Health–funded multicenter randomized clinical trial of statins for the treatment of ARDS was recently stopped for futility.

TABLE 3. Logistic Regression Analysis of Prehospital Aspirin Use and Development of Acute Respiratory Distress Syndrome in All Enrolled Patients ($n = 1,149$)

Model	OR	95% CI	p
Unadjusted	0.719	0.535–0.968	0.030
Adjusted for propensity	0.745	0.532–1.043	0.086
Adjusted for propensity and selected variables[a]	0.659	0.469–0.944	0.023

[a]Selected variables included age, gender, race, sepsis, and Acute Physiology and Chronic Health Evaluation II score.

TABLE 4. Logistic Regression Analysis of Prehospital Aspirin Use and Development of Acute Respiratory Distress Syndrome in Patients With Sepsis ($n = 725$)

Model	OR	95% CI	p
Unadjusted	0.589	0.416–0.835	0.003
Adjusted for propensity	0.602	0.418–0.902	0.018
Adjusted for propensity and selected variables[a]	0.608	0.408–0.905	0.014

[a]Selected variables included age, gender, race, sepsis and Acute Physiology and Chronic Health Evaluation II score.

TABLE 5. Multivariate Logistic Regression Model for Mortality (Aspirin Adjusted by Propensity) in 1,149 Patients

	OR	95% CI	p
Aspirin[a]	0.697	0.468–1.037	0.075
Sepsis	1.445	1.014–2.068	0.043
Acute respiratory distress syndrome	1.768	1.296–2.418	< 0.001
Acute Physiology and Chronic Health Evaluation II score (per 1-point increase)	1.044	1.025–1.064	< 0.001
Age (per 1-yr increase)	1.013	0.994–1.032	0.186
Shock	1.445	1.058–1.974	0.021

[a]Aspirin was adjusted by propensity score.

Currently, there is an ongoing multicenter randomized clinical trial for evaluation of aspirin for prevention of ARDS (NCT01504867). In this study, the first dose of study drug (aspirin vs placebo) is administered within the first 24 hours after presentation to the hospital with a goal of preventing the subsequent development of ARDS in the hospital (31). However, it should be noted that in the current observational study, the majority of the patients (84%) had already developed ARDS on the first ICU day. As such, any medication prescribed only from the beginning of hospitalization may be too late to prevent the majority of occurrences of ARDS, highlighting the difficulties that are encountered in designing prevention studies for ARDS.

This study has both strengths and limitations. Major strengths include the large number of patients and large number of ARDS cases as well as the meticulous prospective phenotyping for ARDS in the VALID cohort. The use of a propensity score for aspirin use in the primary analysis also strengthens the study. A limitation of the study is that the information about prehospital aspirin use was derived from the medical record or from the patients themselves and may not be completely accurate. Second, since aspirin use is indicated for a variety of medical conditions, there may still be factors that influence aspirin use that confound the association between aspirin use and ARDS even after propensity adjustment. Third, we were likely underpowered to demonstrate a dose-effect of aspirin. Tuinman et al (15) showed that high-dose aspirin is superior to low-dose aspirin in preventing ALI in animal study. In our study, high-dose aspirin users had slightly lower prevalence (25%) of ARDS than low-dose users (27.2%), but this finding was not statistically significant ($p = 0.773$). Fourth, it is possible that competing risk of death could confound the primary outcome of ARDS development. However, because the vast majority of patients in the study developed ARDS on the first ICU day (Fig. 2), and patients were excluded if they stayed in the ICU for less than 48 hours, the risk of confounding by competing risk of death is substantially mitigated. Finally, it should be noted that all patients in the current study were enrolled in a single center. Although the VALID study enrolls a very heterogeneous population of critically ill patients with a few exclusions to enrollment, the findings may not be generalizable to other centers that care for a different population.

In summary, in critically ill patients after adjusting for a propensity score for prehospital aspirin use, we found that aspirin use was significantly associated with a lower prevalence of ARDS during the first 4 days of ICU stay. Furthermore, this association was stronger in patients with sepsis compared with other critically ill patients. These findings lend support to the need for prospective clinical trials to determine whether aspirin can prevent the development of ARDS in at-risk patients.

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