

# Aspirin for prevention of acute respiratory distress syndrome (ARDS): let's not throw the baby with the water!

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Kor *et al.* recently published the results of the LIPS-A trial (1). In this national multicenter randomized controlled trial, early aspirin administration (325 mg loading dose then 81 mg/day for 7 days) was compared to placebo in terms of reduction of acute respiratory distress syndrome (ARDS) occurrence during the first week after inclusion of patients at risk for ARDS. Those patients were identified in the emergency department if they had a Lung Injury Prediction Score (LIPS) (2) greater than or equal to four without evidence for ARDS at that time. The main reason for exclusion was a previous treatment with antiplatelet therapy.

A total of 195 patients in each arm were studied. The result of this phase 2b trial was negative: ARDS occurred during the first week in 10.3% (n=20) of the patients in the intervention group versus 8.7% (n=17) in the placebo group (P=0.53). Ventilator-free days at day 28, ICU and hospital lengths of stay and mortality were not different.

As regards safety, the authors did not report any additional harm in the aspirin group, especially bleeding-related adverse events (5.6% *vs.* 2.6%, P=0.13). The blood level of interleukin-2 was higher in the aspirin group (P=0.08). The other inflammatory markers were not different between both groups.

We would like to comment this paper in different areas. We will first discuss about the background of the study and then suggest some reasons that may explain that this trial was negative. We will conclude with some further research thrusts that could be done in this field.

## The background of the study

### Physiological data

Platelets are suspected to play a key role in the pathogenesis of ARDS. Indeed, once activated, platelets may aggregate within the pulmonary circulation and produce neutrophil extracellular traps (NET) that attract leucocytes (3). Activated platelets may also produce pro-thrombotic and pro-inflammatory molecules. In humans, both broncho-alveolar lavage (BAL) and alveolar tissue examination exhibit a pattern of enhanced platelet activation with increased platelet-specific alpha granules in BAL (4) and accumulation of platelet-leucocytes aggregates. The level of platelet activation correlated with the ARDS severity.

Aspirin is an “old” drug, which has been used for decades to relief pain and fever. In the 70's, its capability to inhibit prostaglandin (PGE2) through acetylation of cyclooxygenases (COX) 1 and 2 was demonstrated (5). Other mechanisms of actions have been discovered since then as aspirin can lower the production of thromboxan (TXA2), increase the inhibition of NFκB and increase the production of nitric oxide (NO). These mechanisms are the basic tenets of the anti-inflammatory and anti-platelet aggregation properties of aspirin (3). A new mechanism of action was recently discovered as the production of lipoxin, which plays an anti-inflammatory role (6).

In the ARDS setting, animal studies tended to prove a beneficial effect of aspirin on ARDS prevention. In a murine

model of acute lung injury [(ALI); acid aspiration and sepsis-induced ALI], blocking the platelet pathway through platelet depletion or administering aspirin improved histological findings (namely edema and neutrophils recruitment) and oxygenation (7). In a murine model of transfusion-related ALI, aspirin also prevented lung injury and mortality (8).

In addition to the inherent limits of these models, it should be stressed that aspirin was used at dosage, which was largely supra therapeutic, amounting to 1 mg/g and 100 µg/g, respectively (7,8).

### **Clinical data**

Recent meta-analysis (9) of nine cohort studies concluded that those patients admitted to emergency department or ICU and at risk for ARDS/ALI, who were receiving an antiplatelet drug before hospital admission (e.g., for cardiovascular prevention) had lower risk of mortality (OR 0.61; 95% CI: 0.52–0.71;  $I^2 = 0\%$ ;  $P < 0.001$ ) and ARDS/ALI occurrence (OR 0.64; 95% CI: 0.50–0.82;  $I^2 = 0\%$ ;  $P < 0.001$ ). This association is, however, subject to multiple confusion bias: patients benefiting of antiplatelet therapy have usually a medical monitoring and are likely to be in better health than patients with untreated underlying diseases.

### **Why is this trial negative?**

#### ***The difficulty to predict ARDS***

To date it is still difficult to predict the occurrence of ARDS after risk factor exposure. The LIPS score, used in present study, has a poor predictive performance of ARDS. For a LIPS score  $>4$ , the sensitivity is 69% and the specificity 78% to predict ARDS occurrence. In the validation cohort the positive predictive value was 18%. The adjunction of angiopoietin 2 plasma level improved the prediction of ARDS: positive predictive value 40%, negative predictive value 100% (10).

In the present study, LIPS threshold selected a population where only 9.5% of the patients eventually developed ARDS. Therefore the intervention only impacted a small number of patients ( $n=37$ ). Therefore, present trial may be underpowered to detect an effect from the intervention tested.

#### ***A problem of timing? Dose? Route?***

Even if the patient has not had ARDS at the time of

inclusion, it is likely that the initial insult had already occurred. This latter was the reason leading patients to the emergency department for medical consultation. Therefore, it could be that the platelet activation process was still ongoing at the time of aspirin administration, which was henceforth not early enough.

The dose used in the trial was common and proven to have anti-inflammatory effects. However, low-dose aspirin has been validated in stable patients. One could assume that in a situation of hyper-inflammation, the dose required might be higher. The absence of differences between both groups of the LIPS-A study in terms of inflammatory markers might be explained by this way.

In animal models, the dosing used corresponded to more than 7 g of aspirin for an average human. On the other hand, those patients who will not develop ARDS might be exposed to unbalanced bleeding-related adverse events from the use of high-dose aspirin. This has already been the case with activated C protein (11,12).

The route of administration is of concern too. Indeed, nebulizing the compound would have increased higher regional concentration and produced stronger effect on platelet activity inhibition. However, to date, this pulmonary route is mainly used as a bronchoprovocation test (13) and might be deleterious in unstable patients.

#### ***One ARDS, multiple causes...***

The authors of the study assumed that blockade of the platelet pathway might reduce occurrence of ARDS. ARDS is a syndrome caused by different etiologies: pneumonia, aspiration, extra-pulmonary sepsis, trauma... Whether platelet inhibition might mitigate ARDS evolution in all these situations is not clear, especially in trauma, where aspirin might prevent resolution of local bleeding.

Unfortunately, we do not have the tools to evaluate the role of platelets in the large panel of mechanisms leading to ARDS in a given patient. Hence, giving aspirin to a population of patients at risk for ARDS, even if the prediction tool for ARDS is excellent, might lead to negative results.

### **Let's not throw the baby with the water**

Despite these negative results, this study is important in the field of the ARDS research.

To date, management of ARDS is mainly supportive. Low-tidal volume (14), optimized positive end expiratory

pressure (15), prone position (16), and neuromuscular blocking agents (17) during mechanical ventilation for overt ARDS are interventions that showed benefits on patient outcome from prevention/attenuation of ventilator-induced lung injury. Mortality is, however, still high, around 40% (18).

Any intervention trying to reduce ARDS incidence has to be considered with attention.

Further research is needed in order to:

- (I) Find better tools to predict the progression to ARDS. Indeed, to make the studies more robust and adequately powered, we need to better screen and define the population at risk;
- (II) Better understand the mechanisms of ARDS in a given patient, which is the key for a personalized medicine. Since ARDS is a syndrome and not a disease, different mechanisms can lead to ARDS. It is not clear if there is a common pathway leading to ARDS from various risk factors. However, most of the ARDS are from a pulmonary etiology (i.e., pneumonia and inhalation) and are presumably sharing a same physiopathology.

Multiple drugs are currently tested in phase 2 and phase 3 trials for the prevention of ARDS and recorded in clinicaltrials.gov website. Some of these trials might produce negative results if the questions raised above are not satisfied.

To conclude, we firmly believe that prevention of ARDS is a fundamental research target and should not be put aside. Translation from animal models to clinical benefits will not be easy due to the difficulty to define the target population and the heterogeneity of the ARDS mechanisms. The negative results of the present study should not make us curb our enthusiasm.

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## Footnote

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*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Comment on:* Kor DJ, Carter RE, Park PK, *et al.* Effect of Aspirin on Development of ARDS in At-Risk Patients

Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial. JAMA 2016;315:2406-14.

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