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Aspirin as a Treatment for Acute Respiratory Distress Syndrome: a randomised placebo controlled clinical trial.

Philip Toner PhD[1,2], Andrew J Boyle PhD[1,2], James J McNamee FICM[2], Kathryn Callaghan MB[3], Christopher Nutt PhD[2], Paul Johnston PhD[4], John Trinder PhD[5], Margaret McFarland Msc[2], Rejina Verghis PhD[6], Daniel F McAuley MD[1,2] and Cecilia M O'Kane PhD[1].

Author Details

1) The Wellcome-Wolfson Institute For Experimental Medicine; School of Medicine, Dentistry and Biomedical Sciences; Queen's University Belfast, 97 Lisburn Road, Belfast, BT9 7BL.

2) Royal Victoria Hospital, Belfast Health and Social Care Trust, Grosvenor Road, Belfast BT12 6BA.

3) Altnagelvin Area Hospital, Glenshane Road, Londonderry BT47 6SB.

4) Antrim Area Hospital, Bush Road, Antrim, BT41 2RL.

5) Ulster Hospital, Upper Newtownards Road, Dundonald, Belfast, BT16 1RH

6) Northern Ireland Clinical Trial Unit, 1st floor Elliott Dynes Building, Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA.

Corresponding author- Philip Toner (philip.toner@belfasttrsut.hscni.net)

Declarations

Funding

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Conflicts of interest

The authors have no financial or ethical conflicts of interest regarding the contents of this manuscript.

Ethics approval

This study was preformed in line with the principles of the Declaration of Helsinki, the study was approved by a national research ethics committee 24th October 2014 (14/NI/1093).

Consent to participate

Written consent was obtained from the patient's legal representative and followed up by retrospective consent to continue from the patient if that was possible.

Author's contributions

DFM and CO'K conceived the study. All authors made a substantial contribution to the protocol development and contributed to the running of the trial. All authors have read and approved the manuscript.

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Abstract

Background

There is no pharmacological treatment for the acute respiratory distress syndrome (ARDS). Platelets play an important role in the pathophysiology of ARDS. Pre-clinical, observational and clinically relevant models of ARDS indicate aspirin as a potential therapeutic option.

Research question

Is enteral aspirin 75mg once daily safe and effective in improving surrogate outcomes in adult patients with ARDS?

Study Design and Methods

This randomised, double blind (patient and investigator), allocation concealed, placebo-controlled phase 2 trial was conducted in five UK intensive care units. Patients fulfilling the Berlin definition of ARDS were randomly assigned in a 1:1 ratio to receive enteral aspirin 75mg or placebo, for a maximum of 14 days, using a computer-generated randomisation schedule, with variable block size, stratified by vasopressor requirement. The primary endpoint was oxygenation

index (OI) at day 7. Secondary outcomes included safety parameters and other respiratory physiological markers. Analyses were by intention to treat.

Results

The trial was stopped early, due to slow recruitment, after 49 of a planned 60 patients were recruited. 24 patients were allocated to aspirin and 25 to placebo. There was no significant difference in day 7 OI (unadjusted mean 54.4 [SD 26.8] in aspirin group, 42.4 [SD 25] in placebo group; mean difference 12.0, 95% CI -6.1 to 30.1, p= 0.19). Aspirin did not significantly impact the secondary outcomes. There was no difference in the number of adverse events between the groups (13 in each, odds ratio 1.04, 95% CI 0.56 to 1.94, p=0.56).

Interpretation

Aspirin was well tolerated but did not improve OI or other physiological outcomes, a larger trial is not feasible in its current design.

Trial Registration: NCT02326350 (registration date November 2014)

Word count: 264

Key words

Aspirin, acute respiratory distress syndrome, placebo controlled, clinical trial, randomised control trial, critical care.

Abbreviations

ARDS- acute respiratory distress syndrome, OI- oxygenation index, ATLs- aspirin triggered lipoxins, EVLP- *ex-vivo* lung perfusion, MHRA- Medicines and Health products Regulation Agency, SOFA- sequential organ failure

assessment score, APACHE II- acute physiology and chronic health evaluation II score, SAEs- serious adverse events, VFDs- ventilator free days and HTRP- higher amount of on treatment reactive platelets.

Introduction

The acute respiratory distress syndrome (ARDS) remains a considerable cause of mortality[1] and morbidity[2], with no widely accepted pharmacological treatment[3].

Platelets may play a role in the pathophysiology of ARDS[4-7]. The lungs act as a site for platelet maturation and reservoir for mature platelets[8]. Platelet activation and aggregation recruits additional platelets and leucocytes[9], and promotes the production of aspirin triggered lipoxins (ATLs)[10]. Multiple murine models of ARDS demonstrated that platelet depletion[9], aspirin administration[11] and ATL administration[12] improved various outcomes including reduced neutrophil migration and pulmonary oedema formation and improved survival. While many of these pre-clinical models involved supra- therapeutic systemic doses, several observational studies conclude that low dose aspirin is associated with better outcomes in patients with ARDS[13-18]. Aspirin administration, reduced alveolar inflammation and injury in a human *ex-vivo* lung perfusion (EVLP) model of ARDS and in a healthy volunteer model of endotoxin induced lung injury[19]. Aspirin 75mg was as effective as aspirin

1200mg daily in reducing pulmonary neutrophil infiltration and cytokine production in the healthy volunteer model[19].

Recently, the LIPS-A trial reported that low dose aspirin did not reduce incidence of ARDS within 7 days in patients at high risk (Lung Injury Prediction Score ≥ 4) of developing ARDS[20]. One limitation was the unexpectedly low incidence of ARDS (9.5% compared to the predicted 18%), which limited the ability of the study to detect any statistically significant effect. A subsequent sub-study, investigating lipid mediator and leukocyte responses, concluded that of the 367 patients included 24 developed ARDS following initial administration of the study drug. In this population the incidence of ARDS was numerically (but not statistically significantly) lower in the aspirin treated group (10 vs 14 patients), however as before this sub-study was under-powered[38].

Whilst the LIPS-A trial did not support the use of aspirin in the prevention of ARDS, the STAR (ASpirin as a Treatment for ARDS) study tested the hypothesis aspirin 75mg was an effective treatment option.

Study design and methods

STAR was a randomised, double- blind (patient and investigator), allocation concealed, multi centre, placebo-controlled phase 2 trial to determine if aspirin improved surrogate clinical outcomes and was safe in adult patients with ARDS. The study was approved by a national research ethics committee (14/NI/1093), the Medicines and Health products Regulation Agency (MHRA) (CTA number 32485/0025/001-0001, EudraCT number 2014-002564-32) and

sponsored by the Belfast Health and Social Care Trust (BHSCT). STAR was coordinated through the Northern Ireland Clinical Trials Unit (NICTU).

The trial protocol and statistical analysis plan has been published previously[21]. The report has been prepared in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines[22].

Patients were recruited from five intensive care units (ICUs) across Northern Ireland. Invasive mechanically ventilated patients were eligible within 72 hours of onset of ARDS, as defined by acute onset of hypoxemia with PaO_2/FiO_2 ratio of less than or equal to 40kPa with positive end expiratory pressure (PEEP) of 5cm H_2O or more, bilateral infiltrates on radiograph, not fully explained by pulmonary pathology (Berlin definition of ARDS)[23]. Exclusion criteria included contra-indications to aspirin or antiplatelet therapy, or imminent treatment withdrawal. Full inclusion and exclusion criteria are listed in the online supplement. Several protocol amendments were implemented during the course of the study. The first increased the number of recruiting sites. The initial recruiting site was the tertiary centre for trauma and neurosurgery, which resulted in a high proportion of exclusions due to head injury or major haemorrhage. The additional sites have a more generalised medical and surgical patient population with the expectation this would aid recruitment. The next adjusted the platelet cut-off to less than 50 from less than $100x10^9$/l and the exclusion of patients on methotrexate was limited to those on 15mg or more per week. Finally the exclusion of patients with active or recurrent peptic ulcer disease was limited to active disease within the previous five years.

Written consent was obtained from the patient's legal representative and followed up by retrospective consent to continue from the patient if that was possible. Where consent to continue was not obtained, consent from the legal representative remained valid, as in previous critical care trials[24-26].

Subjects were randomly assigned to receive enteral aspirin 75mg or placebo. Randomisation was stratified by vasopressor use: patients were randomised in a 1:1 ratio using blocks of variable size. Aspirin 75mg and placebo had an identical appearance, were packaged identically and identified only by a unique pack number. An independent clinical trials pharmacist allocated the next sequential number as per the computer-generated randomisation schedule, and was the only person with access to the randomisation schedule. Patients and investigators were blinded to treatment allocation. A member of the ICU nursing staff not involved in the trial administered the study drug.

Patients were given aspirin 75mg capsule or placebo. The dose of aspirin was based on similar dosages of aspirin showing benefit in observational studies[13,15] as well as the fact that low dose aspirin reduced neutrophil mediated inflammation in a human model of ARDS[19]. As the median (IQR) duration for mechanical ventilation in ARDS is 6 (2-12)[27] days, treatment for maximum 14 days was selected to ensure adequate time for the study drug to have effect.

The study drug was continued until the first of the following: 14 days after randomisation, discharge from critical care, death, drug related adverse event (AE), following request from the clinical team or legal representative, on the development of a condition requiring aspirin as treatment or if the haemoglobin dropped below 70g/l.

All patients had baseline demographic data recorded including aetiology and severity of ARDS, Murray Lung Injury Score, sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation II (APACHE II) score. Daily data was collected at or as close to 10:00hrs as possible: these included arterial blood gas, ventilator requirements, SOFA score and clinical laboratory assessments. Plasma, urine and bronchoalveolar lavage samples were collected, when possible, for additional exploratory mechanistic analysis. Clinical care was delivered in accordance with local guidelines.

The primary outcome was oxygenation index (OI) at day 7. OI is a physiological index of the severity of ARDS and measures both impaired oxygenation and the amount of mechanical ventilation delivered. OI (cmH2O/ kPa) is calculated as mean airway pressure (cm H_20) x FiO_2 x 100) ÷ PaO_2 (kPa), therefore a decreasing OI correlates with improving oxygenation. OI has been shown to be predictive of mortality in patients with ARDS[28, 29]. Secondary outcomes were OI on days 4 and 14, respiratory compliance and P/F ratio on days 4, 7 and 14, change in SOFA score from baseline to days 4, 7 and 14. Patients were assessed for AEs up to 28 days after completion of the drug. The duration of ventilation, length of ICU and hospital stay and 28 and 90- day mortality were also recorded. However these are not considered formal outcome measures because the study did not have sufficient power to assess these outcomes.

As the population recruited to the STAR study is already critically ill, it was expected that many of the patients would experience AEs. Events that were expected in this population were not reported as AEs. The summary of product characteristics (SmPC) for aspirin was used as the reference safety

information. All serious adverse events (SAEs) were reported with the outcome and the association with the underlying clinical condition.

Sample size calculations were informed by previous clinical trials evaluating therapies for patients with ARDS[30,25]. The mean (standard deviation; SD) of OI at day 7 in patients with ARDS is 62 (51) cmH_2O/kPa[25]. A sample size of 56 participants had 80% power at a two-tailed significance level of 0.05 to detect a difference of 39 cmH_2O/kPa in OI. Assuming a dropout rate of 3% (in keeping with previous ARDS trials[31]) it was planned to recruit a total of 60 patients. In a previous phase 2 study of similar size, we have found that an intervention can demonstrate a change in OI of a similar magnitude confirming a treatment effect of this size can be achieved[25].

Analyses were on an intention-to-treat basis. The primary outcome measure was OI at day 7. Day 7 was chosen as this time interval will minimise the competing effects of death and extubation, while allowing a sufficient time interval for a biological effect to occur. The primary analysis looked at OI at day 7 using only data available at that specific time point. In order to account for attrition where patients did not have an OI measured at day 7 due to death or extubation, a further analysis of OI at day 7 used the last available data before the patient discontinued from the study to form an imputed day 7 OI. Secondary outcomes were analysed using data available at the specified time point without imputation. Unadjusted analyses used independent t-test. Adjusted analyses were undertaken using Analysis of Covariance (ANCOVA) to adjust for the baseline values. The ventilator free days (VFD) score, duration of mechanical ventilation and length of stay (LOS) outcomes were summarized using median and inter-quartile range (p25 to p75) and tested using Wilcoxon rank-sum test.

The categorical variables were tested using Fisher's exact test. A linear mixed model was used to compare change, over time, in a range of clinical laboratory assessments including full blood picture, renal function and coagulation screen. All available data-points were considered in the model, treatment was the fixed effect and patient was the random effect in the mixed model. This model provides an estimate of fixed effects while adjusting for the non-independence due to repeated measurements on each subject.

Results

Patients were recruited from 10th February 2015 to 25th November 2018. During this 45-month period a total of 593 potential participants were screened with 49 (8.3%) successfully recruited (reason for exclusion listed in supplementary table 1). The Data Monitoring Committee (DMC) reviewed the unblinded data throughout the study and in November 2018 the DMC recommended closure of the study after 49 of the planned 60 patients had been recruited, due to slow recruitment. No safety concerns were highlighted by the DMC, but it was felt to continue the study would not significantly alter the outcome. 24 patients were allocated to the aspirin group and 25 to the placebo group. All patients received their allocated medications and no patient withdrew or was lost to follow up (see figure 1).

The baseline demographic and clinical characteristics for each randomised group are shown in table 1. While the two groups were largely comparable, the aspirin group had more male participants (aspirin 58.3% vs placebo 40%), had a higher baseline APACHE II score (aspirin 24.4 vs placebo 22.0) and a lower vasopressor requirement (aspirin 54.2% vs placebo 64%). The main cause of ARDS was pneumonia, but the placebo group had more sepsis-induced ARDS

than the aspirin group (aspirin 20.8% vs placebo 40%). These differences probably likely represent a chance finding due to the lower than planned sample size.

The median duration (IQR) of treatment was 9 (6-13) days in the aspirin group and 8 (6-14) days in the placebo group (supplementary table 2). The most common reasons for discontinuation of the study drug were completion of the treatment course at day 14 (aspirin 21% vs placebo 36%), occurrence of an AE (aspirin 29% vs placebo 24%), or discharge from critical care (aspirin 29% vs placebo 20%). A total of 8 protocol deviations were recorded. Four patients (1 in aspirin group and 3 in placebo) received an extra dose of the study drug in error, either after it had been discontinued or after the total 14 day course was complete. Two patients (1 aspirin and 1 placebo) had a dose of their study drug omitted in error. Two other protocol deviations are recorded which both involved accidental discarding of the extra study drug instead of the study drug being returned to pharmacy after completion of the study (supplementary table 2).

There was no significant difference between the mean observed OI in the aspirin group (mean 54.4 [SD 26.8]) and the placebo group at day 7 (mean 42.4 [SD 25]; mean difference 12.0, 95% CI -6.1 to 30.1, p= 0.19). OI at day 7 was available for 17 patients in each group (see supplementary table 3 for reasons OI not available). Similarly, there was no significant difference between the mean OI when the last observation was carried forward, in the aspirin (mean 45.7 [27.0]) and the placebo group at day 7 (mean 46.8 [SD 33.8]; mean difference -1.1, 95% CI -18.7 to 16.6, p= 0.90). Furthermore, there was no significant difference in mean observed OI difference between the aspirin and

the placebo group at days 4 and 14. There were no significant differences in respiratory system compliance, PaO_2/FiO_2 ratio, or change in SOFA score between the groups up to day 14 (table 2).

The number of VFDs was not significantly different between the randomised groups (p=0.72) and there was no significant difference in the duration of ventilation (see table 3). The median (IQR) duration of length of stay (LOS) in critical care for all patients was 12.5 days (8- 21.5) for the aspirin group and 15 days (9-27) for the placebo group. The median (IQR) duration of LOS in hospital for all patients was 20.5 days (15-29) for the aspirin group and 26 days (15-67) for the placebo group. When considered separately for survivors and non-survivors, the median ICU (supplementary figure 1a) and hospital (supplementary figure 1b) LOS did not differ between aspirin and placebo treated patients. The overall mortality was 24.5% (n=12, 7 in the aspirin group and 5 in the placebo group), with no significant difference in 28 or 90- day mortality between the groups. For each patient who died, the cause of death resulted from the underlying medical condition (supplementary table 4).

A total of 26 AEs were recorded between the randomised groups (13 in each group), including 5 SAEs (two in the aspirin group and 3 in the placebo group, see supplementary table 5). Only one SAE was related to the study drug (a haemorrhagic stroke), which occurred in the placebo group. The remaining four SAEs included one myocardial infarction (aspirin group) and 3 thrombotic strokes (1 in aspirin group and 2 in placebo group) all of which required aspirin as a treatment. These SAEs were assessed as being unrelated to the study drug and due to the underlying medical condition. The most common AE was a drop in haemoglobin (7 events in aspirin group and 8 in placebo group). There

was no difference in the mean haemoglobin levels up to day 14 (p= 0.94), (supplementary figure 2). Other bleeding related AEs included a subconjunctival haemorrhage (aspirin group), haemoptysis post suction (aspirin group), a small volume of blood found in an ileostomy bag (placebo group) and aspiration of a small volume of blood from the NG tube (aspirin group). The remaining AEs included an increase in ventilation requirements following sedation for a BAL (placebo group) and the development of thrombocytosis requiring aspirin treatment (aspirin group). Measures of renal and liver dysfunction did not differ between the aspirin and placebo treated groups (data not shown).

Thromboxane B2, a marker of platelet activation and degranulation, showed a trend to lower values in the aspirin treated group, but the difference failed to reach statistical significance, p=0.07 (figure 2a). Plasma C-reactive protein (CRP) fell in both groups over time but was higher in the aspirin group at the beginning of the study (figure 2b). When CRP was corrected for baseline values, there was no significant difference between the groups. There was no significant change in peripheral total white cell count, neutrophil count or measured plasma cytokines between the two treatment groups (supplementary table 4) however these are simply exploratory analyses.

Discussion

In this trial investigating aspirin as a treatment for ARDS, there was no significant difference in the primary outcome of OI at day 7. Furthermore, aspirin did not have a significant impact on any of the secondary outcomes.

However, the administration of was well tolerated with a similar number of AEs in both groups.

Several issues need to be considered in interpreting these results. Dose and route of administration may have been limiting factors. In a clinically relevant healthy human volunteer model of ARDS induced by inhaled endotoxin, aspirin 75mg administered orally as a pre-treatment for 7 days, significantly attenuated neutrophil mediated inflammation and reduced thromboxane formation[19]. Importantly in this study, 75mg was no less effective than a dose of 1.2g daily of aspirin. Given that higher doses of aspirin are more likely to result in adverse effects, it was considered appropriate to use 75mg of aspirin in the STAR trial.

However, critically ill patients in ICU often have notably deranged physiology due to disease or organ failure. This, coupled with the influence of organ support or concomitant medications, can alter pharmacokinetics[32,33]. In a study comparing intravenous (i.v.), oral chewable and enteric coated aspirin administration in 66 critically ill patients, plasma concentrations of acetylsalicylic acid and salicylic acid were not only highly variable with oral administration, but also substantially reduced compared to healthy volunteers[33]. Salicylic acid concentrations increased with i.v. use. I.v. administration demonstrated a comparable half life to healthy volunteers suggesting metabolism and elimination were not altered[34]. To compensate for these changes in pharmacokinetics an intravenous form of aspirin might be considered in future clinical trials.

Multiple parameters could be measured to assess the pharmacodynamics including platelet aggregation, but TXB_2 is accepted as an appropriate

surrogate marker for aspirin pharmacodynamics[40]. In a healthy human volunteer model studying the effects of aspirin on platelet-related inflammation in response to LPS, a once daily dose of aspirin (75 mg/24 hours) was sufficient to adequately supress platelet COX activation and downstream thromboxane production similar to effects in cardiovascular prophylaxis[19,35,36]. Critically ill patients already taking aspirin have been reported to have a higher residual thromboxane level compared to cardiology patients on aspirin[34]. Furthermore patients in ICU have a significantly higher amount of on treatment reactive platelets (HTRP) compared to patients taking aspirin for cardiovascular prophylaxis (ICU patients 85% vs cardiovascular prophylaxis patients 20%)[34]. In our trial aspirin was associated with a non-statistically significant trend towards lower concentrations of plasma thromboxane B2 at days 4, and 7 suggesting some minor biological effect, which may not have clinical benefit. The downward trend in TXB_2 the aspirin, but not the placebo, treated group suggests intrinsic aspirin resistance does not account for the absence of efficacy of aspirin in this trial. Unfortunately the variability in plasma thromboxane B2, and the low number of patients, meant the study was underpowered for this measurement. It is possible that although oral low dose aspirin was sufficient to substantially reduce plasma thromboxane B2 in our previous healthy volunteer model of LPS induced pulmonary inflammation in humans[19], in order to compensate for the impact critical illness has on absorption, distribution, platelet turnover, and HTRP rate, a higher, repeated or intravenous dose may be required.

Additional cytokines measured are included in Supplementary table 6. The healthy human volunteer study of aspirin in a model of LPS inhalation[19] showed

a clear anti-inflammatory effect, but there was no signal towards any anti-inflammatory effect in this study. However the number of samples for these cytokines limits any possible conclusions.

As with other ARDS studies, the STAR trial recruited a heterogeneous population with a wide range of aetiologies. Latent class analysis of data from several large randomised control trials [37,38] identified the existence of a hyper-inflammatory and a hypo-inflammatory subphenotypes which differ in clinical and biomarker characteristics as well as in clinical outcomes [38]. A precision medicine approach, identifying the sub-group of patients who might be more treatment responsive to aspirin might be useful.

Finally, failing to achieve the target sample size impacts on the interpretation of the results and has implications for any further trials. Although the final number of recruited patients means the study was underpowered, there is no evidence of a trend towards benefit in any of the physiological markers in response to aspirin. Importantly only 8.3% of the 593 patients who met the criteria for screening were successfully randomised. This potentially limits the generalisability to a wider population of patients and makes the feasibility of a large interventional study of aspirin in ARDS questionable, unless further studies are less restrictive in their exclusion criteria.

One further limitation to highlight is the high number of protocol violations in the study (supplementary table 2). Despite the number of violations we feel these were unlikely to have significant impact on the trial outcome.

Interpretation

Aspirin 75mg daily in patients with ARDS showed no evidence of improvement in physiological markers of pulmonary or systemic dysfunction. These data do not support the use of low dose aspirin in the treatment of ARDS, furthermore the feasibility of a large interventional study of aspirin in ARDS is questionable, unless further studies are less restrictive in their exclusion criteria.

Take Home Point:

Study Question

Is enteral aspirin 75mg once daily safe and effective in improving surrogate outcomes in adult patients with ARDS?

Results

Less than 10% of screened patients were recruited, and the study was terminated early due to slow recruitment. Aspirin was well tolerated but had no benefit on physiological markers of lung injury or systemic organ dysfunction. Aspirin had no effect on systemic inflammatory responses.

Interpretation

Aspirin appeared to be well tolerated in patients with ARDS. However, recruitment was a significantly limited due to exclusion criteria. The feasibility of a large interventional study of aspirin in ARDS is questionable, unless further studies are less restrictive in their exclusion criteria.

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Figure Legends

1. Consort Diagram

2.(A) Plasma thromboxane B2 (TxB2) concentration in aspirin (black line) and placebo (grey line) treated groups over duration of study. Data are mean and SD. N numbers are the number of patients at each time point for which the sample was available to measure TxB2. (B) Plasma CRP in patients treated with aspirin (black line) and placebo (grey line) during the study. Data are mean and SD. N = number of patients in whom CRP was measured at given time point. Mixed effect model p=0.02; adjusted analysis for baseline CRP not significant.

Table 1. Baseline demographics and clinical characteristics

	Aspirin	**Placebo**
Number	24	25
Age- years (SD)	55.4 (12)	56.4 (17.7)
Male sex- no. (%)	14 (58.3)	10 (40)
APACHE II score (SD)	24.4 (7.3)	22.0 (7.7)
Mean arterial pressure- mmHg (SD)	64.3 (7.2)	65.0 (5.3)
Tidal Volume- ml/kg PBW (SD)	7.2 (2.3)	7.6 (2.4)
Vasopressor required- yes no. (%)	13 (54.2)	16 (64.0)
Plateau pressure- cm H2O (SD)	23.5 (6.0)	24.1 (4.9)
Oxygenation index- kPa (SD)	59.3 (30.3)	66.3 (21.0)
Worst PaO2/ FiO2 ratio- kPa (SD)	13.6 (6.4)	13.1 (6.1)
SOFA score (SD)	9.4 (3.3)	10.3 (4.0)
Aetiology of ARDS- no. (%)*		
Smoke/ toxin inhalation	1 (4.2)	2 (8.0)
Gastric content aspiration	6 (25.0)	6 (24.0)
Near drowning	0 (0.0)	0 (0.0)
Thoracic trauma	2 (8.3)	2 (8.0)
Pneumonia	14 (58.3)	13 (52.0)
Sepsis	5 (20.8)	10 (40.0)
Pancreatitis	1 (4.2)	0 (0.0)
Non- thoracic trauma	0 (0.0)	1 (4.0)
Other≠	1 (4.2)	3 (12.0)
No aetiology identified	0	0

Data are n (%) or mean (SD). APACHE II= acute physiology and chronic health evaluation. OI= oxygenation index. SOFA= sequential organ failure assessment.

* Some patients had more than one recorded cause of ARDS, in the aspirin group there were 30 causes of ARDS for 24 patients and in the placebo group there were 37 causes of ARDS for 25 patients. ≠ Other causes include out of hospital cardiac arrest, blood transfusion related and intra abdominal surgery.

Table 2. Outcome measures

	Unadjusted analysis				Adjusted analysis			
	Aspirin (SD; n)	**Placebo (SD; n)**	**Mean difference (95% CI)**	**p ♯**	**Aspirin (SE; n)**	**Placebo (SE; n)**	**Mean difference (95% CI)**	**p ≠**
Primary outcome Day 7 OI – cmH_2O/ kPa								
Day 7 Observed values	54.4 (26.8; n=17)	42.4 (25.0; n=17)	12.0 (-6.1 to 30.1)	0.19	54.5 (6.4; n=17)	42.3 (6.4; n=17)	12.2 (-6.2 to 30.7)	0.19
Day 7 Imputed values*	45.7 (27.0; n=24)	46.8 (33.8; n=25)	-1.1 (-18.7 to 16.6)	0.90	46.8 (6.1; n=24)	45.7 (6.0; n=25)	1.1 (-16.3 to 18.5)	0.90
OI – cmH2O/ kPa								
Day 4	61.4 (36.9; n=22)	54.5 (28.8; n=23)	6.9 (-13.0 to 26.8)	0.49	62.0 (6.9; n=22)	53.9 (6.7; n=23)	8.1 (-11.3 to 27.6)	0.40
Day 14	52.3 (36.6; n=7)	37.4 (24.1; n=10)	14.9 (-16.4 to 46.1)	0.33	52.3 (13.4; n=7)	37.3 (10.8; n=10)	15.0 (-25.5 to 55.4)	0.44
Mean respiratory compliance (l/cmH_2O)								
Day 4	31.5 (24.3; n=9)	24.6 (11.8; n=9)	6.9 (-12.2 to 25.9)	0.46	22.6 (4.4; n=9)	28.1 (4.1; n=9)	-5.5 (-19.1 to 8.1)	0.39
Day 7	65.5 (81.2; n=4)	37.1 (25.4; n=4)	28.3 (-75.7 to 132.4)	0.53	75.5 (46.8; n=4)	39.9 (46.8; n=4)	35.6 (-175.9 to 247.2)	0.63
Day 14	36.5 (n=1)	14.2 (n=1)	22.3 (N/A)	N/A				
Mean PF ratio (kPa)								
Day 4	26.1 (9.2; n=24)	25.9 (9.0; n=23)	0.5 (-4.9 to 5.9)	0.85	25.9 (1.9; n=24)	25.9 (1.9; n=23)	-0.05 (-5.3 to 5.4)	0.99
Day 7	26.8 (9.9; n=21)	30.6 (12.2; n=22)	-3.8 (-10.6 to 3.1)	0.27	26.5 (2.4; n=21)	31.0 (2.3; n=22)	-4.5 (-11.2 to 2.3)	0.19
Day 14	27.7 (9.9; n=10)	28.4 (9.1; n=15)	-1.2 (-9.0 to 6.6)	0.76	26.7 (2.9; n=10)	29.5 (2.3; n=15)	-2.8 (-10.7 to 5.0)	0.46
Change in SOFA score from baseline								
Day 4	-1.3 (2.9; n=22)	-1.9 (2.9; n=21)	0.5 (-1.2 to 2.3)	0.54	-1.4 (0.6; n=22)	-1.8 (0.6; n=21)	0.4 (-1.4 to 2.1)	0.66
Day 7	-2.8 (3.8; n=20)	-4.4 (3.0; n=21)	1.1 (-0.5 to 3.8)	0.13	-2.9 (0.7; n=20)	-4.2 (0.7; n=21)	1.3 (-0.8 to 3.3)	0.23
Day 14	-2.7 (3.6; n=10)	-7.3 (4.0; n=13)	4.6 (1.3 to 7.9)	0.009	-3.8 (1.1; n=10)	-6.4 (0.9; n=13)	2.6 (-0.5 to 5.8)	0.10

Unadjusted and adjusted (for baseline) analysis on outcome measures. For unadjusted data is mean (SD; number of patients analysed), for adjusted data is mean (SE; number of patients analysed). SD or SE not available when n= 1. OI= oxygenation index. SOFA= sequential organ failure assessment.

* Analysis used the last available data before the patient discontinued form the study of data was missing form a specific time point. Other outcomes were analysed using only data available at the specific time point.

♯ p value calculated via t test ≠ p value calculated via ANCOVA

Table 3. Clinical outcomes for each group

	Aspirin	**Placebo**	**p- value**
Median VFD up to day 28 – days (IQR)	16 (0 to 21.5)	15 (0 to 21.5)	0.72
Duration of ventilation			
All patients – days (IQR)	10 (5.5 to 15)	10 (6 to 19)	0.43
Alive patients - days (IQR)	8 (5 to 13) n= 21	9.5 (6 to 21) n= 20	0.37
Deceased patients – days (IQR)	13 (10 to 20) n= 3[#]	15 (9 to 18) n=5	0.88
Length of stay			
Median duration of ICU stay for all patients – days (IQR)	12.5 (8 to 21.5)	15 (9 to 27)	0.51
Median duration of hospital stay for all patients – days (IQR)	20.5 (15 to 29)	26 (15 to 67)	0.51
Mortality			
28 day mortality	6 (25.0 %)	5 (20.0%)	0.74
90 day mortality	7 (29.2 %)	5 (20.0%)	0.52

Data are median (IQR) or n (%). The p values for VFDs, duration of mechanical ventilation and duration of ICU or hospital stay is calculated via Wilcoxon rank sum test. All-cause mortality p values are calculated via fishers exact test. Data was censored at 90 days. VFD= ventilator free days. ([#]3 patients achieve unassisted breathing but died before day 28).

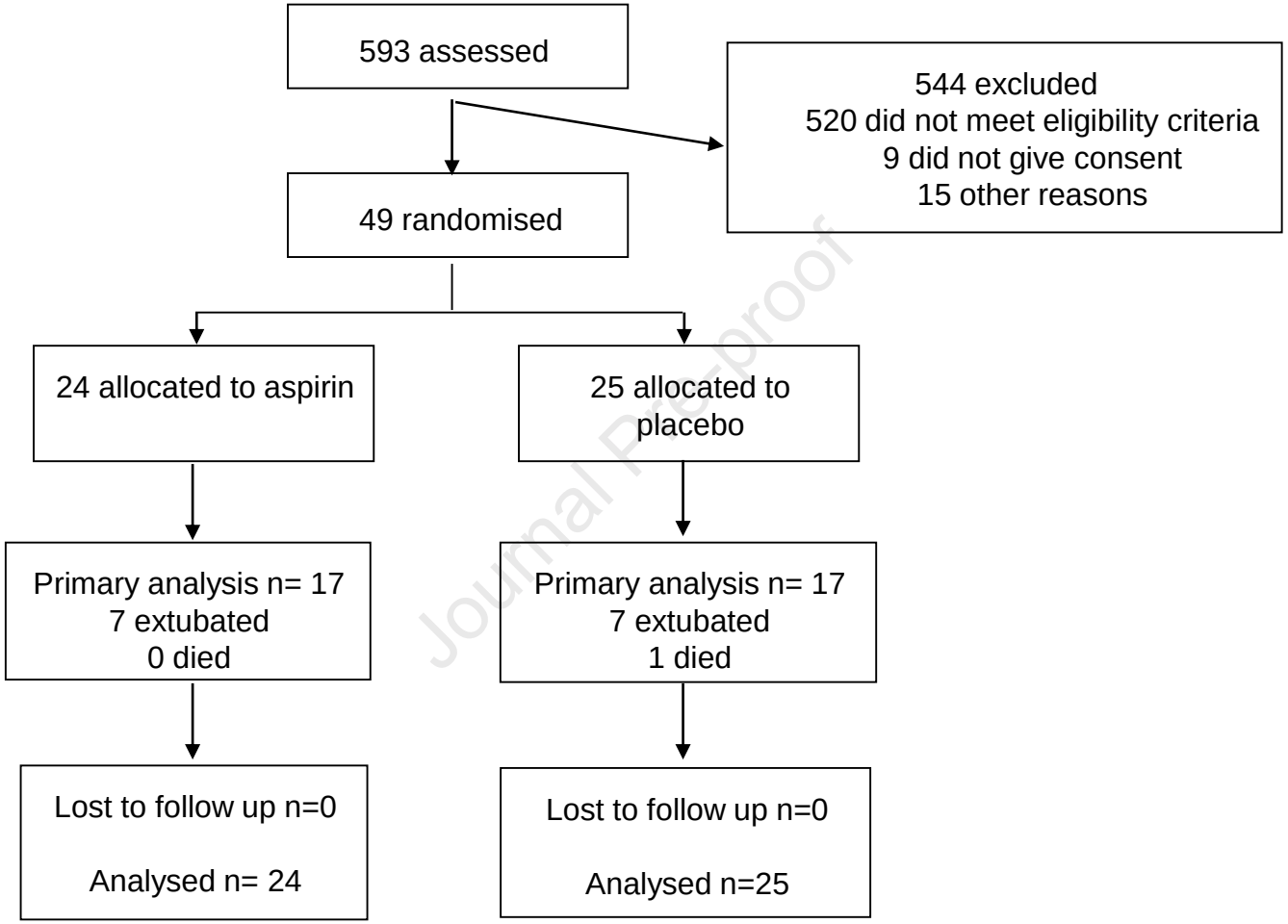

Figure 1 CONSORT diagram

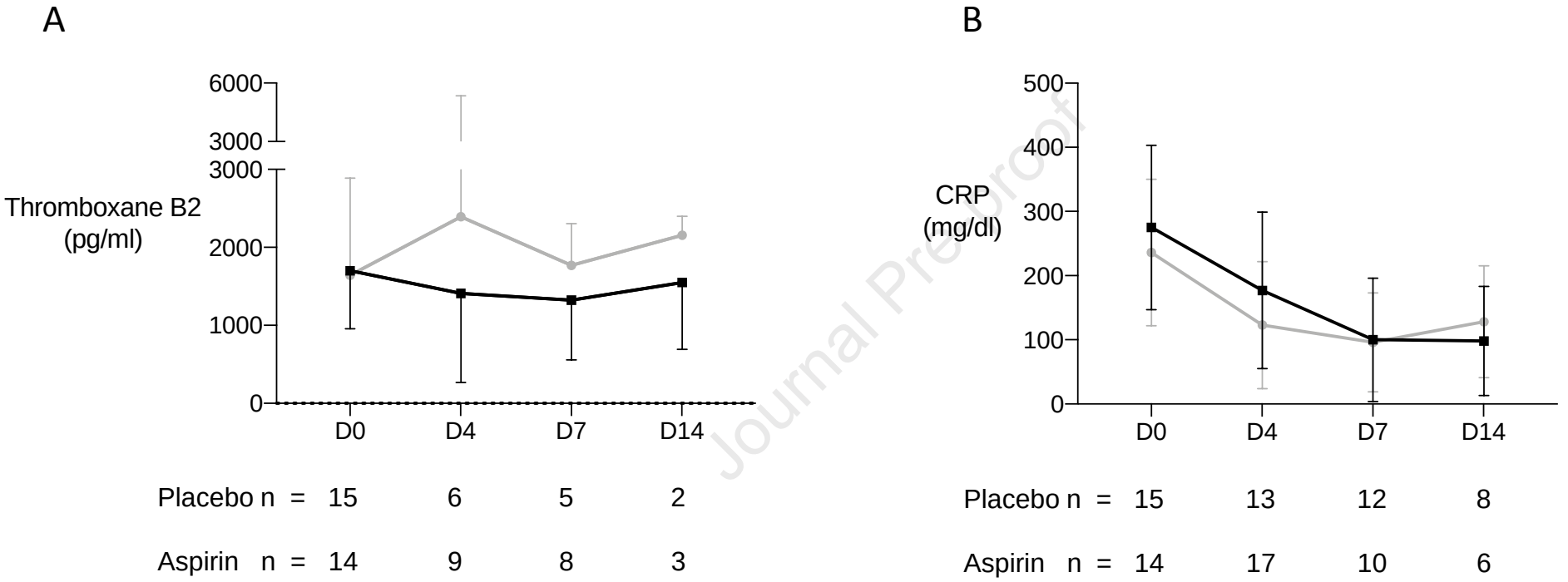

Fig 2 (A) Plasma thromboxane B2 (TxB2) concentration in aspirin (black line) and placebo (grey line) treated groups over duration of study. Data are mean and SD. N numbers are the number of patients at each time point for which the sample was available to measure TxB2. (B) Plasma CRP in patients treated with aspirin (black line) and placebo (grey line) during the study. Data are mean and SD. N = number of patients in whom CRP was measured at given time point. Mixed effect model p=0.02; adjusted analysis for baseline CRP not significant.

Abbreviations

ARDS- acute respiratory distress syndrome, OI- oxygenation index, NETS- neutrophil extracellular trap, ATLs- aspirin triggered lipoxins, EVLP- *ex-vivo* lung perfusion, MHRA- Medicines and Health products Regulation Agency, SOFA- sequential organ failure assessment score, APACHE II- acute physiology and chronic health evaluation II score, SAEs- serious adverse events, VFDs- ventilator free days and HTRP- higher amount of on treatment reactive platelets.