**Table S1. Studies Excluded after Full-text Review**

|  |  |
| --- | --- |
| Author, year  | Reasons for exclusion  |
| Brevard,2008[[1](#_ENREF_1)] | Case report study |
| Griffith,2005[[2](#_ENREF_2)] | Review article |
| Sarma,1990[[3](#_ENREF_3)] | Letter to editor |
| Al Harbi,2016[[4](#_ENREF_4)] | Incidence of newly-developed ARDS not reported；the risk of ARDS not clearly described |
| Tabrizi,2012[[5](#_ENREF_5)] | Incidence of newly-developed ARDS not reported; inclusion of patients younger than 18 years old |
| Zeni,1996[[6](#_ENREF_6)] | Incidence of newly-developed ARDS not reported |
| Bein,1996[[7](#_ENREF_7)] | Lack of a control group with non-antiplatelet therapy; incidence of newly-developed ARDS not reported; |
| Meyer,1998[[8](#_ENREF_8)] | Incidence of newly-developed ARDS not reported; inclusion of patient with developed ARDS at the beginning of the study; lack of a control group with non-antiplatelet therapy; |
| Bacher,1997[[9](#_ENREF_9)] | Lack of a control group with non-antiplatelet therapy; incidence of newly-developed ARDS not reported; |
| Elmer,2013[[10](#_ENREF_10)] | Irrelevant: association between ARDS and antiplatelet therapy not investigated  |
| Bein,2011[[11](#_ENREF_11)] | Irrelevant: association between ARDS and antiplatelet therapy not investigated |
| Eisen,2012[[12](#_ENREF_12)] | Incidence of newly-developed ARDS not reported |
| Harr,2013[[13](#_ENREF_13)] | Incidence of newly-developed ARDS not reported |
| Otto,2013[[14](#_ENREF_14)] | Incidence of newly-developed ARDS not reported; data of a control group with non-antiplatelet therapy not reported |
| Losche,2012[[15](#_ENREF_15)] | Review article |
| Winning,2009[[16](#_ENREF_16)] | Incidence of newly-developed ARDS not reported |
| Winning,2010[[17](#_ENREF_17)] | The risk of ARDS of included patients not clearly described; incidence of newly-developed ARDS not reported |
| Tsai,2015[[18](#_ENREF_18)] | Incidence of newly-developed ARDS not reported |
| Gross,2013[[19](#_ENREF_19)] | Inclusion of patients without high risk of ARDS |
| Locker,1997[[20](#_ENREF_20)] | Investigate prostaglandin E1 which has various effects on ARDS |

**Table S2. Baseline Patient Characteristics of the Randomized Studies**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author/year | Study group | Sample size | Male No. (%) | Age (years)a | Illness severity scores a | Mechanical ventilation No. (%) | SepsisNo. (%) | ShockNo. (%) | PneumoniaNo. (%) | AspirationNo. (%) | TraumaNo. (%) | High risk surgeryNo. (%) | PancreatitisNo. (%) | Massive transfusionNo. (%) |
| Kor.2016[[21](#_ENREF_21)] | InterventionControl | 195195 | 107 (54.9)96 (49.2) | 57.0 (44.0-67.0)57.0 (47.0-68.0) | LIP 6.0(5.0-7.5)LIP 5.5(4.5-7.5) | 39(20.0)b29(14.9)b | 150 (76.9)153 (78.5) | 41 (21.0)40 (20.5) | 120 (61.5)116 (59.5) | 28 (14.4)22 (11.3) | 9 (4.6)15 (7.7) | 01 (0.5) | 1(0.5)0 | -- |
| Vincent,1985[[22](#_ENREF_22)] | Interventioncontrol | 1617 | -- | -- | -- | -- | 5 (31.25)7 (41.2) | 16 (100)17 (100) | -- | -- | 5 (31.3)4 (23.5) | -- | -- | -- |

a Continuous variables reported as mean (standard deviation) or median (interquartile range) unless otherwise indicated.

b Mechanical ventilation reported in randomized day.

**Table S3. Intervention Characteristics of Randomized Studies**

|  |  |  |  |
| --- | --- | --- | --- |
| Author, year | Exposure time of antiplatelet therapy | Antiplatelet drugs | Administration and dose of antiplatelet drugs  |
| Kor, 2016[[21](#_ENREF_21)] | Within 24 hours after presentation to the hospital | Aspirin  | A 325mg loading dose in day one followed by 81mg once daily to day 7 |
| Vincent,1985[[22](#_ENREF_22)] | After an episode of non-cardiogenic circulatory shock | Dipyridamole | Constant iv infusion of 3mg/kg•24h until discharged from ICU or after 7 days |

Abbreviation: ICU intensive care unit, iv intravenous injection

**Table S4. Outcome Data of the Randomized Studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Study group | Sample size | ARDS No. (%)a | ICU mortalityNo. (%) | 28-day mortality No. (%) | Hospital mortality No. (%) | Other reported mortality No. (%) |
| Kor,2016[[21](#_ENREF_21)] | Intervention Control | 195195 | 20 (10.3)17 (8.7) | -- | 18 (9.2)18 (9.2) | 14 (7.2)14 (7.2) | 1-year 45 (23.1)1-year 44 (22.6) |
| Vincent,1985[[22](#_ENREF_22)] | Intervention Control | 1617 | 2 (12.5)0 (0.0) | -- | -- | 6 (37.5)4 (23.5) | -- |

1. ARDS within 7 days.

**Table S5. GREAD Evidence Profile of the Randomized studies**
**Question:** Antiplatelet versus non-antiplatelet for patients at high risk of ARDS
**Settings:** Hospital and/or ICU

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **No of patients** | **Effect** | **Quality** | **Importance** |
|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Antiplatelet versus non-antiplatelet** | **Control** | **Relative(95% CI)** | **Absolute** |
| **Newly-developed ARDS** |
| 2 | randomized trials | serious1 | no serious inconsistency | no serious indirectness | serious2 | none | 22/211 (10.4%) | 17/212 (8%) | OR 1.29 (0.66 to 2.5) | 21 more per 1000 (from 26 fewer to 99 more) | LOW | CRITICAL |
|  | 4.4% | 12 more per 1000 (from 15 fewer to 59 more) |
| **Hospital mortality** |
| 2 | randomized trials | serious1 | no serious inconsistency | no serious indirectness | serious2 | none | 20/211 (9.5%) | 18/212 (8.5%) | OR 1.15 (0.58 to 2.27) | 12 more per 1000 (from 34 fewer to 89 more) | LOW | CRITICAL |
|  | 15.4% | 19 more per 1000 (from 59 fewer to 138 more) |

1 Two of three randomized studies did not state the randomization methods and allocation concealments. (Downgraded for serious risk of bias.)
2 The confidence interval for combined OR included no effect and important harm. (Downgraded for serious imprecision.)

**Table S6. Baseline Patient Characteristics of the Observational Studies**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Study group | Sample size | Male No. (%) | Age (years)a | Illness severity scores a | Mechanical ventilation No. (%) | Sepsis No. (%) | Shock No. (%) | Pneumonia No. (%) | AspirationNo. (%) | TraumaNo. (%) | High risk surgeryNo. (%) | PancreatitisNo. (%) | Massive transfusionNo. (%) |
| Mazzeffi,2015 [[23](#_ENREF_23)] | Anti Non-anti | 181194 | 99 (55.0)114 (58.8) | 72 (64-80)57.0 (47.0-68.0) | -- | -- | -- | -- | -- | -- | -- | 181 (100)194 (100) | -- | -- |
| Chen,2015[[24](#_ENREF_24)] | Anti Non-anti | 287862 | 167 (58.2)464 (53.8) | 67 (61-74)58 (50-65) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Valerio,2013 [[25](#_ENREF_25)] | Anti Non-anti | 272379 | 160 (58.8)202 (53.3) | 75.2 (65.2-82.5)65.8 (53.2-78.3) | APACHEⅢ 57.5 (46.0-74.8)APACHEⅢ 55.0 (42.0-68.0) | -- | 272 (100)379 (100) | -- | -- | -- | -- | -- | -- | -- |
| Kor,2011[[26](#_ENREF_26)] | Anti Non-anti | 9762879 | 541 (55.4)1574 (54.7) | 70 (59-81)51 (38-66) | APACHEⅡ 12 (8-16)LIPS 2.5 (1.5-4.0)APACHEⅡ 9 (5-14)LIPS 2.5 (1.5-4.0) | -- | 443 (45.4)1306 (45.4) | 91 (9.3)274 (9.5) | 391 (40.1)834 (29.0) | 52 (5.3)151 (5.2) | 170 (17.4)768 (26.7) | -- | 68 (7.0)240 (8.3) | -- |
| Erlich,2011[[27](#_ENREF_27)] | Anti Non-anti | 7982 | 42 (53.2)44 (53.7) | 77(12)66(19) | APACHEⅢ 46 (34-57)LIPS 3 (1.5-4.0)APACHEⅢ 39 (27-54)LIPS 3 (1.5-4.0) | 8 (10.1)11 (13.4) | 19 (24.1)25 (30.5) | 40 (50.6)47 (57.3) | 30 (38.0)25 (30.5) | 11 (13.9)8 (9.8) | 4 (5.1)4 (4.9) | -- | 2 (2.5)2 (2.4) | -- |
| Ahmed,2014 [[28](#_ENREF_28)] | Case Control | 414414 | 245 (59)245 (59) | 66 (17)66 (17) | LIPS 2 (1-3)LIPS 2 (1-3) | -- | 121 (29)121 (29) | 75 (18)49 (12) | 83 (20)103 (25) | 14 (3)14 (3) | 24 (6)16 (4) | 77 (19)77 (19) | 10 (2)14 (3) | -- |
| Tuinman,2012 [[29](#_ENREF_29)] | CaseControl | 109109 | -- | -- | APACHEⅡ 22 (8)APACHEⅡ 19 (8) | 94 (86)80 (73) | 36 (33)20 (18) | -- | -- | -- | -- | 32 (31)36 (33) | -- | 37 (34)16 (15) |

a Continuous variables reported as mean (standard deviation) or median (interquartile range) unless otherwise indicated.

Abbreviations: LIPS Lung Injury Prediction Score, APACHE Acute Physiology and Chronic Health Evaluation, Anti antiplatelet therapy, Non-anti non-antiplatelet therapy

**Table S7. Intervention Characteristics of the Observational Studies**

|  |  |  |  |
| --- | --- | --- | --- |
| Author, year | Exposure time of antiplatelet therapy | Antiplatelet drugs | Administration and dose of antiplatelet drugs  |
| Mazzeffi,2015[[23](#_ENREF_23)] | Preoperative use (within 5 days of surgery) | Aspirin | Preoperative aspirin was taken by 181 patients (48.3%) with the majority of patients taking 81 mg/d (72%). |
| Chen,2015[[24](#_ENREF_24)] | Prehospital aspirin use | Aspirin | 92 (31%) patients were taking 325mg per day. 184 (64%) patients were taking 81mg per day. In 11 patients the dose was not available. |
| Valerio,2013[[25](#_ENREF_25)] | Documentation of use or administration of antiplatelet therapy at the time of ICU admission | Aspirin, clopidogrel | The main antiplatelet drug used was aspirin as a single drug (88.6%) or in combination with clopidogrel (9.9%). Only 1.5% patients used clopidogrel. Antiplatelet therapy was discontinued in 48 (17.6%) of the patients who received it before ICU admission. Aspirin dose, mg, median (IQR) 81 (81-81). |
| Kor,2011[[26](#_ENREF_26)] | Before hospitalization | Aspirin | Not reported.  |
| Erlich,2011[[27](#_ENREF_27)] | Documentationof use or administration in the medical record of antiplatelet therapyat the time of hospital admission | Aspirin, clopidogrel bisulfate, anagrelide | 68 patients were taking an ASA-containing medication alone, 3 patients were receiving clopidogrel bisulfate alone, and 1 patient was receiving the antiplatelet agent anagrelide. 7 patients were being treated with both ASA and clopidogrel bisulfate. |
| Ahmed,2014[[28](#_ENREF_28)] | During the at-risk period | Aspirin, abciximab, cilostazol, clopidogrel, dipyridamole, eptifibatide, ticlopidine  | Not reported. |
| Tuinman,2012[[29](#_ENREF_29)] | At the time of ICU admission | Aspirin, clopidogrel | All patients used aspirin with an average dose of 80 or 100 mg once a day, 2 patients were also taking clopidogrel. |

Abbreviation: ICU intensive care unit, ASA acetylsalicylic acid

**Table S8. Outcome Data of the Observational Studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Study group | Sample size | ARDS  | ICU mortalityNo. (%) | 28-day mortality No. (%) | Hospital mortality No. (%) | Other reported mortality No. (%) |
| Mazzeffi,2015[[23](#_ENREF_23)] | Anti Non-anti | 181194 | 9 (5.0)12 (6.7) | -- | -- | -- | -- |
| Chen,2015[[24](#_ENREF_24)] | Anti Non-anti  | 287862 | 77 (27)284(33) | -- | -- | Adjust OR 0.697  |  |
| Valerio,2013[[25](#_ENREF_25)] | Anti Non-anti | 272379 | 57 (21.0)132 (34.8) | 26 (9.6)46 (12.1) | -- | 57 (21.0)98 (25.9) | -- |
| Kor,2011[[26](#_ENREF_26)] | Anti Non-anti | 9762879 | 44 (4.5)196 (6.8) | 39 (4.0)134 (4.7) | -- | 63 (6.5)180 (6.3) | -- |
| Erlich,2011[[27](#_ENREF_27)] | Anti Non-anti | 7982 | 10 (12.7)23 (28.1) | 9 (11.4)9 (11.0) | -- | 10 (12.7)13 (15.9) | -- |
| Ahmed,2014[[28](#_ENREF_28)] | CaseControl | 414414 | -- | -- | -- | -- | -- |
| Tuinman,2012[[29](#_ENREF_29)] | CaseControl | 109109 | -- | -- | -- | -- | -- |

Abbreviations: Anti antiplatelet therapy, Non-anti non-antiplatelet therapy

**Table S9. Risk of Bias in the Observational Studies**

|  |
| --- |
| **Cohort studies** |
| Study | Selection | Comparability | Outcome | Total score |
| Exposed Cohort | Non-exposed Cohort | Ascertainment of exposure | Outcome of interest | Assessment of outcome | Length of follow-up | Adequacy of follow-up |
| Mazzeffi,2015[[23](#_ENREF_23)] | \* | \* | \* | \* | \*\* | \* | 0 | 0 | 7 |
| Chen,2015[[24](#_ENREF_24)] | \* | \* | \* | \* | \*\* | \* | 0 | 0 | 7 |
| Valerio,2013[[25](#_ENREF_25)] | \* | \* | \* | 0 | \*\* | \* | 0 | 0 | 6 |
| Kor,2011[[26](#_ENREF_26)] | \* | \* | \* | \* | \*\* | \* | 0 | 0 | 7 |
| Erlich,2011[[27](#_ENREF_27)] | \* | \* | \* | \* | \*\* | \* | \* | 0 | 8 |
| **Case-control studies** |
| Study  | Selection | Comparability | Exposure | Total score |
| Definition adequate | Representativeness | Selection of Controls | Definition of Controls | Ascertainment of exposure | Ascertainment for cases and controls | Non-Response rate |
| Ahmed,2014[[28](#_ENREF_28)] | \* | \* | \* | \* | 0 | \* | \* | 0 | 6 |
| Tuinman,2012 [[29](#_ENREF_29)] | \* | \* | \* | \* | \*\* | \* | \* | 0 | 8 |

**Table S10. GREAD Evidence Profile of the Cohort Studies**
**Question:** Should Antiplatelet therapy be used for patients at high risk of ARDS?
**Settings:** Hospital and/ICU

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **No of patients** | **Effect** | **Quality** | **Importance** |
|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Antiplatelet therapy** | **Control** | **Relative(95% CI)** | **Absolute** |
| **Newly-developed ARDS** |
| 5 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 197/1795 (11%) | 647/4396 (14.7%) | OR 0.63 (0.52 to 0.75) | 49 fewer per 1000 (from 33 fewer to 65 fewer) | LOW | CRITICAL |
|  | 28.1% | 83 fewer per 1000 (from 54 fewer to 112 fewer) |
| **Hospital mortality1** |
| 4 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 179/1434 (12.5%) | 490/4202 (11.7%) | not pooled1 | not pooled1 | LOW | CRITICAL |
|  | 19.5% | not pooled |
| **ICU mortality** |
| 3 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious2 | none | 74/1327 (5.6%) | 189/3340 (5.7%) | OR 0.84 (0.63 to 1.11) | 9 fewer per 1000 (from 20 fewer to 6 more) | VERY LOW | CRITICAL |
|  | 11% | 16 fewer per 1000 (from 38 fewer to 11 more) |

1 The data of both groups were not accessible in Chen and his colleagues' study and therefore it failed to calculate assumed risks and corresponding risks.
2 The confidence interval for combined OR included no effect and important harm.(Downgraded for serious imprecision.)

**Table S11. GREAD Evidence Profile of the Case-control Studies**
**Question:** Should Antiplatelet therapy be used for patients at high risk of ARDS?
**Settings:** Hospital and/or ICU

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **No of patients** | **Effect** | **Quality** | **Importance** |
|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Antiplatelet therapy** | **Control** | **Relative(95% CI)** | **Absolute** |
| **Newly-develop ARDS** |
| 2 | observational studies1 | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 523 cases 523 controls | OR 0.90 (0.85 to 0.95) | - | LOW |  |
|  | 0.0% | - |

1 Case-control

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