Supplemental table 1. Estimates of thrombotic events in primary prevention studies with low dose aspirin (LDA) in women with a history of obstetric antiphospholipid syndrome only and high-risk aPL profile (with or without systemic lupus erythematosus).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** |
| Lefevre 201122 | retrospective cohort | Single treatment arm | LDA | na | 32 | na | 4 (12.5%) | na |
| Cuadrado 201423 | RCT | Single treatment arm | LDA | na | 82 | na | 4 (4.9%) | na |
| Gris 201224 | prospective cohort | Single treatment arm | LDA | na | 517 | na | 68 venous (13.1%); 15 arterial (2.9%) | na |

RCT = randomized controlled trial; na = not applicable.

Supplemental table 2. Estimates of thrombosis recurrence and major bleeding events in single treatment arm studies of different intensities of oral anticoagulation in patients with antiphospholipid syndrome and previous venous thrombosis.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | | **Number of patients, control** | **Events, intervention** | **Events, control** |
| **Recurrent thrombosis** | |  |  |  |  |  | |  |  |
| Derksen 199330 | retrospective cohort | Single treatment arm | warfarin INR 2.5 – 4 | na | 69.5 py | na | | 1.4/100 py | na |
| Munoz-Rodriguez 199932 | retrospective cohort | Single treatment arm | warfarin INR 2.5 – 3.5 | na | 25 | na | | 2 (8%) | na |
| Wittkowsky 200634 | retrospective cohort | Single treatment arm | warfarin INR 3 – 4 (in 72% of patients) | na | 62.5 py | na | | 9.6/100 py | na |
| Giron-Gonzalez 200435 | retrospective cohort | Single treatment arm | warfarin INR 2.5 – 3.5 | na | 628 py | na | | 2.0/100 py | na |
| Schulman 199831 | one arm of RCT | Single treatment arm | na | warfarin INR 2 – 3 | na | 272 py | | na | 7.3/100 py |
| Krnic-Barrie 199733 | retrospective cohort | Single treatment arm | na | warfarin INR 2 – 3.5 | na | 63 py | | na | 4.8/100 py arterial; 0/100 py venous |
| Petrovic 199836 | retrospective cohort | Single treatment arm | na | warfarin INR 2.5 – 3.0 | na | 24 | | na | 9 (37.5%) |
| Tarr 200716 | prospective cohort | Single treatment arm | na | warfarin INR 2.5 – 3 | na | 79 | | na | 6 (7.6.%) |
| Vlachoyiannopoulos  199437 | retrospective cohort | Single treatment arm | na | warfarin INR 2 – 2.6 | na | 15 py | | na | 20/100 py |
|  |  |  |  |  |  |  | |  |  |
| **Major bleeding** | |  |  |  |  |  | |  |  |
| Derksen 199330 | retrospective cohort | Single treatment arm | warfarin INR 2.5 – 4 | na | 69.5 py | na | | 2.8/100 py | na |
| Wittkowsky 200634 | retrospective cohort | Single treatment arm | warfarin INR > 3 (in 72% of patients) | na | 62.5 py | na | | 3.2/100 py | na |
| Giron-Gonzalez 200435 | retrospective cohort | Single treatment arm | warfarin INR 2.5 – 3.5 | na | 628 py | na | | 0.6/100 py | na |
| Krnic-Barrie 199733 | retrospective cohort | Single treatment arm | na | warfarin 2 – 3.5 | na | 63 py | | na | 3.1/100 py |

RCT = randomized controlled trial; INR = international normalized ratio; na = not applicable; py = patient-years.

Supplemental table 3. Estimates of thrombosis recurrence and major bleeding events in studies of direct acting oral anticoagulants (DOAC) in patients with definite antiphospholipid syndrome and first provoked venous thrombosis.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | **Relative effect (95% CI)** | **Study Quality** |
| **Recurrent thrombosis** | | | | | | | | | | |
| Goldhaber 201638 | RCT | Direct | Dabigatran | Warfarin | 71 | 80 | 3 (4.2%) | 4 (5.0%) | HR 0.43 (0.08 - 2.38) | Low risk of bias |
| Cohen 201639 | RCT | Direct | Rivaroxaban | Warfarin | 57 | 58 | 0 | 0 | RR not estimable | High risk of bias |
| Pengo 201840 | RCT | Direct | Rivaroxaban | Warfarin | 59 | 61 | 7 (12%) | 0 | RR 15.5 (0.91 - 266) | Unclear risk of bias |
|  |  | | | | | | | | |  |
| Noel 201541 | case series | Single treatment arm | DOAC | na | 14 | na | 1 (7.1%) | na | na | na |
| Haladyj 201642 | case series | Single treatment arm | DOAC | na | 7 | na | 0 | na | na | na |
| Malec 201743 | case series | Single treatment arm | DOAC | na | 20 | na | 0 | na | na | na |
| Resseguier 201744 | case series | Single treatment arm | DOAC | na | 19 | na | 1(5.2%) | na | na | na |
|  |  |  |  |  |  |  |  |  |  |  |
| **Major bleeding** | | | | | | | | | | |
| Goldhaber 201638 | RCT | Direct | Dabigatran | Warfarin | 71 | 80 | 1 (1.4%) | 2 (2.6%) | HR 0.46 (0.05 - 5.43) | Low risk of bias |
| Cohen 201639 | RCT | Direct | Rivaroxaban | Warfarin | 57 | 58 | 0 | 0 | RR not estimable | High risk of bias |
| Pengo 201840 | RCT | Direct | Rivaroxaban | Warfarin | 59 | 61 | 4 (7%) | 2 (3%) | RR 2.07 (0.39 – 10.87) | Unclear risk of bias |
|  |  | | | | | | | | |  |
| Noel 201541 | case series | Single treatment arm | DOAC | na | 14 | na | 0 | na | na | na |
| Haladyj 201642 | case series | Single treatment arm | DOAC | na | 7 | na | 0 | na | na | na |
| Malec 201743 | case series | Single treatment arm | DOAC | na | 20 | na | 0 | na | na | na |
| Resseguier 201744 | case series | Single treatment arm | DOAC | na | 19 | na | 0 | na | na | na |

RCT = randomized controlled trial; CI = confidence interval; HR = hazard ratio; RR = risk ratio; na = not applicable.

Supplemental table 4. Estimates of thrombosis recurrence and major bleeding events in studies of the duration of anticoagulation in patients with unprovoked venous thrombosis.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | **Relative effect (95% CI)** | **Study Quality** |
| **Recurrent thrombosis** | | | | | | | | | |  |
| Schulman 199846 | RCT | Direct | 4 years of oral anticoagulation | 6 months of oral anticoagulation | 19 | 15 | 1 (5.3%) | 3 (20%) | na | High risk of bias |
| Ginsburg 199547 | retrospective cohort | Direct | long-term anticoagulation | 3-6 months of oral anticoagulation | 4 | 11 | 0 | 2 (18%) | na | Intermediate quality |
| Subtotal |  | Direct |  |  | 23 | 26 | 1 | 5 | RR = 0.33 (0.06 - 1.81); I2 = 0% |  |
| Pengo 201048 | retrospective cohort | Indirect | long-term anticoagulation | discontinuation  anticoagulation | 123 | 37 | 36 (29.2%) | 19 (51.3%) | na | Intermediate quality |
| Hernandez-Munoz 201349 | retrospective cohort | Indirect | long-term anticoagulation | discontinuation  anticoagulation | 39 | 56 | 10 (25.6%) | 37 (57.1%) | na | Intermediate quality |
| Taraborelli 201750 | retrospective cohort | Indirect | long-term anticoagulation | discontinuation  anticoagulation | 55 | 29 | 27 (49%) | 18 (62%) | na | Intermediate quality |
| Total |  | Direct and indirect |  |  | 236 | 136 | 74 | 77 | RR = 0.54 (0.42 - 0.70); I2 = 9% |  |
|  |  | | | | | | | | |  |
| Comarmond 201751 | retrospective cohort | Single treatment arm | na | discontinuation of anticoagulation | na | 25 | na | 6 (24%) | na | na |
|  |  |  |  |  |  |  |  |  |  |  |
| **Major bleeding** | | | | | | | | | |  |
| Pengo 201048 | retrospective cohort | Indirect | long-term anticoagulation | discontinuation  anticoagulation | 123 | 37 | 7 (5.7%) | 1 (2.7%) | RR = 2.11 (0.27 - 16.57) | Intermediate quality |

RCT = randomized controlled trial; RR = risk ratio; CI = confidence interval; na = not applicable.

Supplemental table 5. Estimates of thrombosis recurrence in studies of treatment with vitamin K antagonists versus low dose aspirin (LDA) in patients with definite antiphospholipid syndrome and first arterial thrombosis. RR = risk ratio; CI = confidence interval; na = not applicable.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | **Relative effect (95% CI)** | **Study quality** |
| **Recurrent thrombosis** | |  |  |  |  |  |  |  |  |  |
| Verro 199855 | prospective cohort | Direct | Warfarin | LDA | 7 | 18 | 1 (14.2%) | 7 (39%) | RR 0.37 (0.05 - 2.47) | Intermediate quality |
| Wang 201656 | retrospective cohort | Indirect | Vitamin K antagonist | LDA | 49 | 14 | 15 (30.6%) | 8 (57%) | na | Intermediate quality |
| Total |  | Direct and indirect |  |  | 56 | 32 | 16 | 15 | RR 0.50 (0.26 - 0.93); I2 = 0% |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Derksen 200357 | prospective cohort | Single treatment arm | na | LDA | na | 8 | na | 3 (37.5%) | na | na |

RR = risk ratio; CI = confidence interval; na = not applicable.

Supplemental table 6. Estimates of thrombosis recurrence and major bleeding events in mixed treatment and single arm studies of different intensities of oral anticoagulation in patients with definite antiphospholipid syndrome and first arterial thrombosis.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | |
| **Recurrent thrombosis** | | | | | | | | | |
| Rivier 199464 | retrospective cohort | Mixed treatment | warfarin INR ≥ 3.0 + LDA | warfarin INR 2 – 3 + LDA | 30 py | 23.8 py | 0 | | 16.8/100 py |
| Ruiz-Irastorza 200265 | retrospective cohort | Single treatment arm | warfarin INR 3 – 4 | na | 66.0 py | na | 9.0/100 py | | na |
| Wittkowsky 200634 | retrospective cohort | Single treatment arm | warfarin INR 3 – 4 (in 72% of patients) | na | 62.5 py | na | 9.6/100 py | | na |
| Giron-Gonzalez 200435 | retrospective cohort | Single treatment arm | warfarin INR 2.5 – 3.5 | na | 628 py | na | 2.0/100 py | | na |
| Krnic-Barrie 199733 | retrospective cohort | Single treatment arm | na | warfarin INR 2 – 3.5 | na | 63 py | na | | 4.8/100 py arterial; 0/100 py venous |
| Petrovic 199836 | retrospective cohort | Single treatment arm | na | warfarin INR 2.5 – 3.0 | na | 24 | na | | 9 (37.5%) |
| Tarr 200716 | prospective cohort | Single treatment arm | na | warfarin INR 2.5 – 3 | na | 79 | na | | 6 (7.6%) |
| Vlachoyiannopoulos  199437 | retrospective cohort | Single treatment arm | na | warfarin INR 2 – 2.6 | na | 15 py | na | | 20/100 py |
|  |  |  |  |  |  |  |  | |  |
| **Major bleeding** | | | | | | | | | |
| Ruiz-Irastorza 200265 | Retrospective cohort | Single treatment arm | warfarin INR 3 – 4 | na | 66.0 py | na | 6.0/100 py | na | |
| Wittkowsky 200634 | Retrospective cohort | Single treatment arm | warfarin INR > 3 (in 72% of patients) | na | 62.5 py | na | 3.2/100 py | na | |
| Giron-Gonzalez 200435 | Retrospective cohort | Single treatment arm | warfarin INR 2.5 – 3.5 | na | 628 py | na | 0.6/100 py | Na | |
| Krnic-Barrie 199733 | retrospective cohort | Single treatment arm | na | warfarin INR 2 – 3.5 | na | 63 py | na | 3.1/100 py | |

INR = international normalized ratio; LDA = low dose aspirin; py = patient-years; na = not applicable.

Supplemental table 7. Pregnancy outcomes in studies of low dose aspirin (LDA) treatment in pregnant women (with or without systemic lupus

erythematosus) with high-risk aPL profile but no history of thrombosis or pregnancy complications.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | **Relative effect (95% CI)** | **Study Quality** |
| **Live Births** | | | | | | | | | | |
| Kaaja 199368 | RCT | Direct | LDA | placebo | 2 | 4 | 2 (100%) | 4 (100%) | RR 1.00 | High risk of bias |
| Cowchock 199780 | RCT | Indirect | LDA | no treatment | 11 | 8 | 10 (90.9%) | 8 (100%) | na | High risk of bias |
| Kahwa 200670 | RCT | Indirect | LDA | placebo | 28 | 20 | 27 (96.4%) | 20 (100%) | na | Unclear risk of bias |
| Del Ross 201371 | retrospective cohort | Indirect | LDA | no treatment | 47 | 18 | 45 (95.7%) | 17 (94.4%) | na | Intermediate quality |
| Total |  | Direct and indirect |  |  | 88 | 50 | 84 | 49 | RR 0.98 (0.90 - 1.07); I2 = 0% |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | | |  |
| Kahwa 200670 | RCT | Indirect | LDA | placebo | 28 | 20 | 0 (0%) | 0 (0%) | na | Unclear risk of bias |
| Del Ross 201371 | retrospective cohort | Indirect | LDA | no treatment | 47 | 18 | 4 (8.5%) | 0 (0%) | RR 3.50 (0.20 - 63.0) | Intermediate quality |

RCT = randomized controlled trial; RR = risk ratio; CI = confidence interval; na = not applicable.

Supplemental table 8. Pregnancy outcomes in mixed treatment and single treatment arm studies of low dose aspirin (LDA) and heparin in pregnant women with definite antiphospholipid syndrome and a history of three recurrent spontaneous abortions at or before the 10th week of gestation.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** |
| **Live births** | | | | | | | | |
| Cowchock 199280 | RCT | Mixed treatment | LDA + UFH | LDA + prednisone | 12 | 8 | 9 (75%) | 6 (75%) |
| Pattison 200081 | RCT | Mixed treatment | LDA | no treatment | 20 | 20 | 16 (80 %) | 17 (85 %) |
| Stephenson 200482 | RCT | Mixed treatment | LDA + LMWH | LDA + UFH | 13 | 13 | 9 (69.2%) | 4 (30.8%) |
| Ghosh 200883 | retrospective cohort | Mixed treatment | LMWH | UFH | 9 | 23 | 9 (100%) | 16 (69.6%) |
| Dadhwal 201184 | retrospective cohort | Mixed treatment | LDA + heparin (enoxaparin 40 mg od or UFH 5000 bd) | no treatment/previous pregnancies | 42 | 130 | 36 (85.7%) | 6 (4.6%) |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 69 (86%) | 44 (72%) |
| Rodger 201486 | RCT | Mixed treatment | LMWH | no LMWH | 12 | 10 | 4 (33%) | 3 (30%) |
| Alijotas-Reig 201887 | retrospective cohort | Mixed treatment | LDA + UFH | no treatment | 213 | 35 | 175 (82.1%) | 18 (51.4%) |
| Backos 199988 | retrospective cohort | Single treatment arm | LDA + heparin | na | 150 | na | 107 (71%) | na |
| Pauzner 200189 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 46 | na | 40 (87 %) | na |
| Diejomaoh 200290 | retrospective cohort | Single treatment arm | LDA + heparin | IVIG + LDA + heparin | 36 | 7 | 30 (83%) | 7 (100%) |
| Noble 200591 | prospective cohort | Single treatment arm | LDA + LMWH | UFH+LDA | 25 | 25 | 21 (84%) | 20 (80%) |
| Jeremic 200592 | prospective cohort | Single treatment arm | LDA + LMWH | IVIG+ LDA + heparin | 20 | 20 | 17 (85%) | 18 (90%) |
| Stone 200593 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 30 (91%) | na |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 47 (81%) | na |
| Glasnovic 200795 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 36 | na | 35 (97.2%) | na |
| Heilmann 200896 | retrospective cohort | Single treatment arm | LDA + heparin | IVIG + LDA + heparin | 78 | 43 | 59 (74.3%) | 36 (83.7%) |
| Serrano 200997 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 67 | na | 57 (85.1%) | na |
| Mo 200998 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 35 | na | 28 (80%) | na |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 56 (93%) | na |
| Fouda 2010100 | RCT | Single treatment arm | LDA + enoxaparin 40 mg | LDA + enoxaparin 20 mg | 30 | 30 | 23 (76.7%) | 21 (70%) |
| Simchen 2011101 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 55 | na | 45 (82%) | na |
| Lefevre 201122 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 23 | na | 16 (71%) | na |
| De Carolis 2012102 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 47 | na | 43 (91.5%) | na |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 25 (100%) | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na | 357 (69%) | na |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 20 (80%) | na |
| Rezk 2016106 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 162 | na | 124 (76.5%) | na |
| Latino 2017107 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 106 | na | 88 (83%) | na |
|  |  |  |  |  |  |  |  |  |
| **Miscarriages** | | | | | | | | |
| Backos 199988 | prospective cohort | Single treatment arm | LDA + heparin | na | 150 | na | 28 (18.7%) | na |
| Heilmann 200896 | retrospective cohort | Single treatment arm | LDA + heparin | IVIG + LDA + heparin | 78 | 43 | 5 (6.4%) | 3 (6.9%) |
| Mo 200998 | retrospective cohort | Single treatment arm | LDA + low dose enoxaparin (20 mg) | na | 35 | na | 7 (20%) | na |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 4 (7%) | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | no treatment | 517 | 796 | 91 (17.7%) | 175 (22.1%) |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA+ LMWH | na | 25 | na | 3 (12%) | na |
| Latino 2017107 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 106 | na | 11 (10.4%) | na |
|  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | |
| Cowchock 199280 | RCT | Mixed treatment | LDA + UFH | LDA + prednisone | 12 | 8 | 25% | 100% |
| Pattison 200081 | RCT | Mixed treatment | LDA | no treatment | 16 | 17 | 2 (12.5%) | 0 |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 3 (3.75%) | 2 (3.3%) |
| Backos 199988 | prospective cohort | Single treatment arm | LDA + heparin | na | 150 | na | 26 (24%) | na |
| Jeremic 200592 | prospective cohort | Single treatment arm | LDA + LMWH + IVIG | LDA + LMWH | 20 | 20 | 2 (10%) | 4 (20%) |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 8 (13.8%) | na |
| Serrano 200997 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 67 | na | 12 (21%) | na |
| Fouda 2010100 | RCT | Single treatment arm | LDA + LMWH 40 mg | LDA + LMWH 20 mg | 30 | 30 | 3 (10%) | 2 (9.5%) |
| Lefevre 201122 | retrospective cohort | Single treatment arm | LDA +LMWH | na | 16 | na | 3/16 (18.8%) | na |
| De Carolis 2012102 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 47 | na | 53.40% | na |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 3 (12%) |  |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 5 (20%) | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na | 89 (24.9%) | na |
| Latino 2017107 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 106 | na | 11 (10.4%) | na |
|  |  |  |  |  |  |  |  |  |
| **Pre-eclampsia** | | | | | | | | |
| Cowchock 199280 | RCT | Mixed treatment | LDA + UFH | LDA + prednisone | 12 | 8 | 0 | 3 (37.5%) |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 1 (1.25%) | 0 |
| Jeremic 200592 | prospective cohort | Single treatment arm | LDA + LMWH + IVIG | LDA + LMWH | 20 | 20 | 0 | 3 (15%) |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 3 (5.1%) | na |
| Heilmann 200896 | retrospective cohort | Single treatment arm | LDA + heparin | LDA + heparin + IVIG | 78 | 43 | 9 (11.5%) | 1 (2.3%) |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 4 (7%) | na |
| Fouda 2010100 | RCT | Single treatment arm | LDA + LMWH 40 mg | LDA + LMWH 20 mg | 30 | 30 | 3 (10%) | 2 (6.7%) |
| Mekinian 2012103 | retrospective study | Single treatment arm | LDA + LMWH | na | 25 | na | 0 |  |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na | 40 (10.3%) | na |
| Rezk 2016106 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 162 | na | 31 (21%) | na |
| Latino 2017107 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 106 | na | 5 (5%) | na |
|  |  |  |  |  |  |  |  |  |
| **Maternal thrombosis** | | | | | | | | |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 0 | 0 |
| Pauzner 200189 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 46 | na | 6 (14%) | na |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 0 | na |
| Simchen 2011101 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 55 | na | 7 (12.7%) | na |
| Rezk 2016106 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 162 | na | 28 (17.2%) | na |
|  |  |  |  |  |  |  |  |  |
| **Intrauterine growth retardation** | | | | | | | | |
| Dadhwal 201184 | RCT | Mixed treatment | LDA + heparin (enoxaparin 40 mg od or UFH 5000 bd) | no treatment | 42 | 130 | 9 (21.4%) | na |
| Backos 199988 | prospective cohort | Single treatment arm | LDA + heparin | na | 150 | na | 22 (14.7%) | na |
| Stone 200593 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 4 (11%) | na |
| Jeremic 200592 | prospective cohort | Single treatment arm | LDA + LMWH + IVIG | LDA + LMWH | 20 | 20 | 2 (10%) | 2 (10%) |
| Fouda 2010100 | RCT | Single treatment arm | LDA + LMWH 40 mg | LDA + LMWH 20 mg | 30 | 30 | 2 (6.7%) | 1 (3.3%) |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 3 (12%) | na |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 5 (20%) | na |
| Latino 2017107 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 106 | na | 6 (6%) | na |

RCT = randomized controlled trial; UFH = unfractionated heparin; LMWH = low molecular weight heparin; IVIG = intravenous immunoglobulin; na = not applicable.

Supplemental table 9. Pregnancy outcomes in mixed treatment and single treatment arm studies of low dose aspirin (LDA) and heparin in

pregnant women with definite antiphospholipid syndrome and a history of fetal loss.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** |
| **Live births** | | | | | | | | |
| Cowchock 199280 | RCT | Mixed treatment | LDA + UFH | LDA + prednisone | 12 | 8 | 9 (75%) | 6 (75%) |
| Stephenson 200482 | RCT | Mixed treatment | LDA + LMWH | LDA + UFH | 13 | 13 | 9 (69.2%) | 4 (30.8%) |
| Ghosh 200883 | RCT | Mixed treatment | LMWH | UFH | 9 | 23 | 9 (100%) | 16 (69.6%) |
| Dadhwal 2011 7784 | RCT | Mixed treatment | LDA + heparin (enoxaparin 40 mg od or UFH 5000 bd) | No treatment/previous pregnancies | 42 | 130 | 36 (85.7%) | 6 (4.6%) |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 69 (86%) | 44 (72%) |
| Rodger 201486 | RCT | Mixed treatment | LMWH | no LMWH | 12 | 10 | 4 (33%) | 3 (30%) |
| Alijotas-Reig 201887 | retrospective cohort | Mixed treatment | LDA + UFH | no treatment | 213 | 35 | 175 (82.1%) | 18 (51.4%) |
| Font, 1991111 | retrospective cohort | Single treatment arm | LDA | na | 5 | na | 4 (80%) | na |
| Branch 2000112 | RCT | Single treatment arm | LDA + heparin + IVIG | LDA + heparin + placebo | 7 | 9 | 7 (100%) | 9 (100%) |
| Venkat-Raman 2001113 | prospective cohort | Single treatment arm | LDA + LMWH | na | 170 | na | 164 (96.5%) | na |
| Pauzner 200189 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 46 | na | 40 (87 %) | na |
| Bats 2004114 | prospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 31 (94%) | na |
| Stone 200593 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 30 (91%) | na |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 47 (81%) | na |
| Glasnovic 200795 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 36 | na | 35 (97.2%) | na |
| Serrano 200997 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 67 | na | 57 (85.1%) | na |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 56 (93%) | na |
| Simchen 2011101 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 55 | na | 45 (82%) | na |
| Calderon 2011115 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 25 (100%) | na |
| Lefevre 201122 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 23 | na | 16 (71%) | na |
| Ruffatti 2011116 | prospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 32 (97%) | na |
| De Carolis 2012102 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 47 | na | 43 (91.5%) | na |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 25 (100%) | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na | 357 (69%) | na |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 20 (80%) | na |
| Rezk 2016106 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 162 | na | 124 (76.5%) | na |
|  |  |  |  |  |  |  |  |  |
| **Miscarriage** | | | | | | | | |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na |  | na |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na |  | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na |  | na |
|  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | |
| Branch 2000112 | RCT | Single treatment arm | LDA + heparin + IVIG | LDA + heparin + placebo | 7 | 9 | 7 (100%) | 3 (33%) |
| Venkat-Raman 2001113 | prospective cohort | Single treatment arm | LDA + LMWH | na | 170 | na | 21 (13%) | na |
| Bats 2004114 | prospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 8 (24.2%) | na |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 8 (13.8%) | na |
| Serrano 200997 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 67 | na | 12 (21%) | na |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 14 (25%) | na |
| Calderon 2011115 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 2 (8%) | na |
| Ruffatti 2011116 | prospective cohort | Single treatment arm | LMWH in increasing dose during progression of pregnancy + standard LDA | na | 32 | na | 1 (3.1%) | na |
| Lefevre 201122 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 16 | na | 3/16 (18.8%) | na |
| De Carolis 2012102 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 47 | na | 25 (53.4%) | na |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 3 (12%) | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na | 89 (24.9%) | na |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 5 (20%) | na |
|  |  |  |  |  |  |  |  |  |
| **Pre-eclampsia** | | | | | | | | |
| Cowchock 199280 | RCT | Mixed treatment | LDA + UFH | LDA+prednisone | 12 | 8 | 0 | 3 (3.75%) |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 1 (1.25%) | 0 |
| Venkat-Raman 2001113 | prospective cohort | Single treatment arm | LDA + LMWH | na | 170 | na | 7 (4.1%) | na |
| Bats 2004114 | prospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 1 (3%) | na |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 3 (5.1%) | na |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 4 (7%) | na |
| Calderon 2011115 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 3 (12%) | na |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 0 | na |
| Bouvier 2014104 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 517 | na | 40 (10.3%) | na |
| Rezk 2016106 | retrospective cohort | Single treatment arm | LDA + LMWH (prophylactic) | na | 162 | na | 31 (21%) | na |
|  |  |  |  |  |  |  |  |  |
| **Maternal thrombosis** | | | | | | | | |
| Alalaf 201285 | RCT | Mixed treatment | LMWH | LDA | 80 | 61 | 0 | 0 |
| Pauzner 200189 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 46 | na | 6 (14%) | na |
| A/Magid 200794 | prospective cohort | Single treatment arm | LDA + UFH | na | 58 | na | 0 | na |
| Simchen 2011101 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 55 | na | 7 (12.7%) | na |
| Rezk 2016106 | retrospective cohort | Single treatment arm | LDA + LMWH (prophylactic) | na | 162 | na | 28 (17.2%) | na |
|  |  |  |  |  |  |  |  |  |
| **Intrauterine growth retardation** | | | | | | | | |
| Dadhwal 201184 | retrospective cohort | Mixed treatment | LDA + heparin (enoxaparin 40 mg od or UFH 5000 bd) | no treatment/previous pregnancies | 42 | 130 | 9 (21.4%) | na |
| Branch 2000112 | RCT | Single treatment arm | LDA+heparin+IVIG | LDA+heparin+placebo | 7 | 9 | 1 (14%) | 3 (33%) |
| Bats 2004114 | prospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 7 (21.2%) | na |
| Stone 200593 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 33 | na | 4 (11%) | na |
| Mekinian 2012103 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 3 (12%) | na |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 5 (20%) | na |

RCT = randomized controlled trial; UFH = unfractionated heparin; LMWH = low molecular weight heparin; na = not applicable.

Supplemental table 10. Pregnancy outcomes in studies of low dose aspirin (LDA) and heparin in pregnant women with definite antiphospholipid

syndrome and a history of deliver before 34 weeks gestation due to severe pre-eclampsia or placental insufficiency.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | **Relative effect (95% CI)** | **Study Quality** |
| **Live Births** | | | | | | | | | | |
| van Hoorn 2016117 | RCT | Indirect | LDA + LMWH | LDA | 16 | 16 | 14 (87.5%) | 16 (100%) | na | High risk of bias |
| Munoz-Rodriguez 199932 | retrospective cohort | Indirect | LDA + LMWH | LDA | 12 | 18 | 10 (83%) | 14 (78%) | na | High quality |
| Total |  | Indirect |  |  | 28 | 34 | 24 | 30 | RR 0.96 (0.79 - 1.16);  I2 = 0% |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Pauzner 200189 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 46 | na | 40 (87 %) | na | na |  |
| Glasnovic 200795 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 36 | na | 35 (97.2%) | na | na |  |
| Fawad 201099 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 60 | na | 56 (93%) | na | na |  |
| De Carolis 2012102 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 47 | na | 43 (91%) | na | na |  |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 20 (80%) | na | na |  |
| Rodger 201486 | RCT | Single treatment arm | LMWH | no LMWH | 12 | 10 | 4 (33%) | 3 (30%) | na |  |
| Saccone 2017118 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 631 | na | 357 (56.6%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Miscarriages** | | | | | | | | | | |
| Fawad 201099 | retrospective study | Single treatment arm | LDA + LMWH | na | 60 | na | 4 (7%) | na | na |  |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 3 (12%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | | | |
| van Hoorn 2016117 | RCT | Indirect | LDA + LMWH | LDA | 16 | 16 | 3 (18.8%) | 2 (12.5%) | RR = 1.50 (0.29, 7.81) | High risk of bias |
|  |  |  |  |  |  |  |  |  |  |  |
| Fawad 201099 | retrospective study | Single treatment arm | LDA + LMWH | na | 60 | na | 14 (25%) | na | na |  |
| De Carolis 2012102 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 47 | na | 25 (53.4%) | na | na |  |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 5 (20%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-eclampsia** | | | | | | | | | | |
| Fawad 201099 | retrospective study | Single treatment arm | LDA + LMWH | na | 60 | na | 4/56 (7%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Maternal thrombosis** | | | | | | | | | | |
| van Hoorn 2016117 | RCT | Indirect | LDA + LMWH | LDA | 16 | 16 | 0 | 0 | RR not estimable | High risk of bias |
|  |  |  |  |  |  |  |  |  |  |  |
| Pauzner 200189 | retrospective cohort | Single treatment arm | LDA + LMWH | na | 46 | na | 6 (14%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Intrauterine growth retardation** | | | | | | | | | | |
| Cetkovic 2014105 | prospective cohort | Single treatment arm | LDA + LMWH | na | 25 | na | 5 (20%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Small for gestational age** | | | | | | | | | | |
| van Hoorn 2016117 | RCT | Indirect | LDA + LMWH | LDA | 16 | 16 | 3 (18.8%) | 3 (18.8%) | RR 1.00 (0.24 - 4.23) | High risk of bias |

RCT = randomized controlled trial; LMWH = low molecular weight heparin; na = not applicable.

Supplemental table 11. Prevalence of post-partum maternal thrombosis with continuation or no continuation of heparin after delivery in

women with antiphospholipid syndrome.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** |
| Branch 1992120 | retrospective cohort | Single treatment arm | Heparin in post-partum | na | 29 | na | 1 (3.4%) | na |
| Cowchock 199280 | randomized controlled trial | Single treatment arm | Heparin for 6 weeks post-partum | na | 10 | na | 0 (0%) | na |
| Kutteh 1996121 | controlled trial | Single treatment arm | Heparin for 2-3 weeks post-partum | na | 25 | na | 0 (0%) | na |
| Lima 199673 | Retrospective cohort | Single treatment arm | LMWH for 6 weeks post-partum | na | 23 | na | 0 (0%) | na |
| Granger 1997122 | retrospective cohort | Single treatment arm | LMWH for 6 weeks post-partum | na | 16 | na | 1 (6.2%) | na |
| Serrano 200997 | retrospective cohort | Single treatment arm | LMWH for 4-6 weeks post-partum | na | 67 | na | 0 (0%) | na |
| Ruffatti 2011116 | prospective cohort | Single treatment arm | LMWH for 6 weeks post-partum | na | 33 | na | 0 (0%) | na |
| Fischer-Betz 2012123 | Retrospective cohort | Single treatment arm | LMWH for 6 weeks post-partum | na | 20 | na | 1 (5%) | na |
| Van Hoorn 2016117 | randomized controlled trial | Single treatment arm | LMWH for 6 weeks post-partum | na | 16 | na | 0 (0%) | na |
| Triolo 2003124 | randomized controlled trial | Single treatment arm | na | LMWH stopped at week 37 | na | 19 | na | 0 (0%) |
| Laskin 200975 | randomized controlled trial | Single treatment arm | na | LMWH stopped at week 35 | na | 45 | na | 0 (0%) |
| Dendrinos 2009125 | randomized controlled trial | Single treatment arm | na | LMWH stopped at week 37 | na | 40 | na | 0 (0%) |

RCT = randomized controlled trial; LMWH = low molecular weight heparin; na = not applicable.

Supplemental table 12. Pregnancy outcomes in studies of treatment with hydroxychloroquine (HCQ), low dose prednisolone, or intravenous immunoglobulin (IVIG) in patients with a history of recurrent pregnancy complications despite treatment with low dose aspirin (LDA) and prophylactic dose heparin.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** | **Relative effect (95% CI)** | **Study Quality** |
| **Addition of hydroxychloroquine** | | | | | | | | | |  |
| **Live Births** | | | | | | | | | | |
| Mekinian 2015126 | retrospective pre-post | Direct | HCQ + LDA  + LMWH | LMWH  +/- LDA | 14 | 14 | 10 (71.4%) | 5 (35.7%) | RR 2.0 (0.92 - 4.35) | Intermediate  quality |
| Sciascia 2016127 | retrospective cohort | Mixed treatment | HCQ + LDA  +/- LMWH (72%) | LDA  +/- LMWH (79%) | 51 | 119 | 34 (66.7%) | 60 (57.1%) | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Miscarriage** | | | | | | | | | | |
| Sciascia 2016127 | retrospective cohort | Mixed treatment | HCQ + LDA  +/- LMWH (72%) | LDA  +/- LMWH (79%) | 51 | 119 | 1 (2%) | 13 (10.9%) | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | | | |
| Sciascia 2016127 | retrospective cohort | Mixed treatment | HCQ + LDA  +/- LMWH (72%) | LDA  +/- LMWH (79%) | 51 | 119 | 2 (3.9%) | 16 (13.4%) | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-eclampsia** | | | | | | | | | | |
| Sciascia 2016127 | retrospective cohort | Mixed treatment | HCQ + LDA  +/- LMWH (72%) | LDA  +/- LMWH (79%) | 51 | 119 | 1 (2%) | 8 (6.7%) | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Addition of low-dose prednisolone in the first trimester** | | | | | | | | | |  |
| **Live Births** | | | | | | | | | | |
| Bramham 2011128 | retrospective cohort | Direct | LDA + LMWH + prednisolone | LDA + LMWH | 23 | 93 | 14 (61%) | 4 (4%) | RR 14.1 (5.1 - 39.0) | High quality |
|  | | | | | | | | | | |
| **Addition of IVIG with or without plasma exchange** | | | | | | | | | | |
| **Live Births** | | | | | | | | | | |
| Diejomaoh 200290 | retrospective cohort | Direct | IVIG  (LDA+heparin) | LDA + heparin | 7 | 36 | 7 (100%) | 30 (83.3%) | na | Intermediate  quality |
| Jeremic 200592 | prospective cohort | Direct | IVIG + LDA  + LMWH | LDA + LMWH | 20 | 20 | 18 (90%) | 17 (85%) | na | Intermediate  quality |
| Heilmann 2008130 | retrospective cohort | Direct | IVIG + LDA  + heparin | LDA + heparin | 43 | 78 | 36 (83.7%) | 59 (74.3%) | na | Intermediate  quality |
| Total |  | Direct |  |  | 70 | 134 | 61 | 106 | RR 1.10 (0.97 - 1.25); I2 = 0% |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Branch 2000112 | RCT | Mixed treatment | IVIG + LDA  + heparin | LDA + heparin + placebo | 7 | 9 | 7 (100%) | 9 (100%) | na |  |
| Triolo 2003124 | RCT | Mixed treatment | IVIG | LDA + LMWH | 21 | 19 | 12 (57%) | 16 (84%) | na |  |
| Dendrinos 2009125 | RCT | Mixed treatment | IVIG | LDA + LMWH | 38 | 40 | 15 (39.5%) | 29 (72.5%) | na |  |
| Vaquero 2001131 | prospective cohort | Mixed treatment | IVIG | LDA + Prednisolone | 53 | 29 | 41 (77.3%) | 22 (75.9%) | na |  |
| Ruffatti 201479 | retrospective cohort | Mixed treatment | IVIG + plasmapheresis (7), IVIG alone(5),  plasmapheresis alone (4), IVIG and low-dose prednisolone (3), IVIG+IA (2) | LDA + LMWH | 21 | 104 | 18 (85.7%) | 81 (77.8%) | na |  |
| Ruffatti 2015132 | prospective cohort | Mixed treatment | IVIG + plasma exchange | plasma exchange | 14 | 4 | 13 (92.8%) | 2 (50%) | na |  |
| Marzusch 1996133 | prospective cohort | Single treatment arm | IVIG | none | 38 | na | 31 (81.6%) | na | na |  |
| Heilmann 200196 | retrospective cohort | Single treatment arm | IVIG + LDA  + heparin | none | 17 | na | 16 (94%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Miscarriages** | | | | | | | | | | |
| Heilmann 2008130 | retrospective cohort | Direct | IVIG + LDA  + heparin | LDA + heparin | 43 | 78 | 3 (6.9%) | 5 (6.4%) | RR 1.09 (0.27 - 4.34) | Intermediate  quality |
| Dendrinos 2009125 | RCT | Mixed treatment | IVIG | LDA + LMWH | 38 | 40 | 11 (39%) | 21 (52%) |  |  |
| Triolo 2003124 | RCT | Mixed treatment | IVIG | LDA + LMWH | 21 | 19 | 6 (29%) | 2 (11.0%) | na |  |
| Marzusch 1996133 | prospective cohort | Single treatment arm | IVIG | none | 38 | na | 4 (10.5%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | | | |
| Jeremic 200592 | prospective study | Direct | IVIG + LDA  + LMWH | LDA + LMWH | 20 | 20 | 2 (10%) | 4 (20%) | RR 0.50 (0.10 - 2.43) | Intermediate  quality |
| Branch 2000112 | RCT | Mixed treatment | IVIG + LDA  + heparin | LDA + heparin + placebo | 7 | 9 | 1 (14.3%) | 3 (33%) | na |  |
| Vaquero 2001131 | prospective cohort | Mixed treatment | IVIG | LDA +  Prednisolone | 53 | 29 | 9.00% | 5.00% | na |  |
| Triolo 2003124 | RCT |  | IVIG | LDA + LMWH | 21 | 19 | 1 (4.7%) | 0 | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Pre-eclampsia** | | | | | | | | | | |
| Jeremic 200592 | prospective cohort | Direct | IVIG + LDA  + LMWH | LDA + LMWH | 20 | 20 | 0 | 3 (15%) | na | Intermediate  quality |
| Heilmann 2008130 | retrospective cohort | Direct | IVIG + LDA  + heparin | LDA + heparin | 43 | 78 | 1 (2.3%) | 9 (11.5%) | na | Intermediate  quality |
| Total |  | Direct |  |  | 63 | 98 | 1 | 12 | RR 0.18 (0.03 - 0.95); I2 = 0% |  |
| Heilmann 200196 | retrospective cohort | Single treatment arm | IVIG + LDA  + LMWH | none | 17 | na | 3 (18%) | na | na |  |
|  |  |  |  |  |  |  |  |  |  |  |
| **Intrauterine growth retardation** | | | | | | | | | | |
| Jeremic 200592 | prospective cohort | Direct | IVIG + LDA  + LMWH | LDA + LMWH | 20 | 20 | 2 (10%) | 2 (10%) | RR 1.00 (0.16 - 6.42) | Intermediate  quality |
| Branch 2000112 | RCT | Mixed treatment | IVIG + LDA  + heparin | LDA + heparin + placebo | 7 | 9 | 1 (14%) | 3 (33%) | na |  |

RCT = randomized controlled trial; RR = risk ratio; CI = confidence interval; LMWH = low molecular weight heparin; na = not applicable; IA = immunoadsorption.

Supplemental table 13. Pregnancy outcomes in single treatment arm studies of pregnant women with thrombotic antiphospholipid syndrome

treated with low dose aspirin (LDA) and therapeutic dose low molecular weigth heparin (LMWH).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Design** | **Comparison** | **Intervention** | **Control** | **Number of patients, intervention** | **Number of patients, control** | **Events, intervention** | **Events, control** |
| **Live births** | | | | | | | | |
| Stone 200593 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 33 | na | 30 (91%) | na |
| Bramham 2010129 | retrospective cohort | Single treatment arm | LDA+ LMWH therapeutic dose | na | 41 | na | 41 (100%) | na |
| Fischer-Betz 2012123 | prospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 23 | na | 21 (91.3%) | na |
| Ruffatti 201479 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 55 | na | 39 (71%) | na |
| Saccone 2017118 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 119 | na | 50 (42.0%) | na |
|  |  |  |  |  |  |  |  |  |
| **Pre-term delivery** | | | | | | | | |
| Bramham 2010129 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 41 | na | 11 (26.8%) | na |
| Fischer-Betz 2012123 | prospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 23 | na | 9 (42.9%) | na |
|  |  |  |  |  |  |  |  |  |
| **Pre-eclampsia** | | | | | | | | |
| Bramham 2010129 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 41 | na | 10 (24.4%) | na |
| Fischer-Betz 2012123 | prospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 23 | na | 8 (34.8%) | na |
|  |  |  |  |  |  |  |  |  |
| **Maternal thrombosis** | | | | | | | | |
| Fischer-Betz 2012123 | prospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 23 | na | 3 (13%) | na |
|  |  |  |  |  |  |  |  |  |
| **Intrauterine growth retardation** | | | | | | | | |
| Stone 200593 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 33 | na | 4 (11%) | na |
| Fischer-Betz 2012123 | prospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 23 | na | 6 (28.6%) | na |
|  |  |  |  |  |  |  |  |  |
| **Small for gestational age** | | | | | | | | |
| Bramham 2010129 | retrospective cohort | Single treatment arm | LDA + LMWH therapeutic dose | na | 41 | na | 16 (39.5%) | na |

na = not applicable