**S2 Table: Primary outcome and prespecified subgroups analysis**

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| --- | --- |
| **Outcomes** | **Low and unknown risk studies** |
| **n** | **References** | **Random effect model** | **Fixed effect model** | **Homogeneity** |
| **SMD** | **95 % CI (p value)** | **SMD** | **95 % CI (p value)** | **P value** | **I2 (%)** |
| **Primary outcome** |
| Exercise capacity | 9 | [3, 4, 15, 16, 18, 20-22, 24] | 0.36 | 0.02-0.70 (p=0.04) | 0.21 | 0.06-0.36 (p=0.007) | <0.001 | 77 |
| 6MWT | 4 | [3, 20, 21, 24] | MD: 12.97 | -23.27- 49.20 (p=0.48) | MD: 10.46 | -11.45-32.38 (p=0.35) | 0.08 | 56 |
| VO2 max | 4 | [4, 15, 16, 18] | MD: 2.34 | 0.52-4.16 (p=0.01) | MD: 2.73 | 1.94-3.51 (p<0.001) | 0.02 | 71 |
| Treadmill | 1 | [22] | MD: -1.00 | -52.70-50.70 (p=0.97) | MD:-1.00 | -52.70-50.70 (p=0.97) | N/A | N/A |
| **Classes PH-targeted therapy** |
| PDE-5i | 7 | [3, 4, 15, 16, 18, 20, 21] | 0.50 | 0.04-0.95 (p=0.03) | 0.29 | 0.11-0.47 (p=0.002) | <0.001 | 81 |
| ERA | 2 | [22, 24] | 0.01 | -0.27-0.29 (p=0.96) | 0.01 | -0.27-0.29 (p=0.96) | 0.89 | 0 |
| sGC stimulators | 0 | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Prostanoids | 0 | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **Pulmonary hypertension** |
| With PH | 4 | [4, 16, 20, 24] | 0.27 | -0.03-0.56 (p=0.08) | 0.27 | -0.03-0.56 (p=0.08) | 0.55 | 0 |
| Without PH/Unknown | 5 | [3, 15, 18, 21, 22] | 0.43 | -0.11-0.98 (p=0.12) | 0.19 | 0.01-0.36 (p=0.04) | <0.001 | 88 |
| **Left ventricular ejection fraction** |
| Preserved | 3 | [4, 21, 22] | 0.15 | -0.05-0.35 (p=0.15) | 0.15 | -0.05-0.35 (p=0.15) | 0.52 | 0 |
| Reduced | 5 | [3, 15, 16, 18, 20] | 0.66 | -0.10-1.42 (p=0.09) | 0.34 | 0.09-0.60 (p=0.009) | <0.001 | 87 |
| Both | 1 | [24] | 0.04 | -0.46-0.53 (p=0.89) | 0.04 | -0.46-0.53 (p=0.89) | N/A | N/A |
| **Study duration** |
| ≤ 6 months | 4 | [3, 4, 20, 24] | 0.06 | -0.27-0.40 (p=0.70) | 0.01 | -0.23-0.26 (p=0.91) | 0.16 | 41 |
| > 6 months | 5 | [15, 16, 18, 21, 22] | 0.60 | 0.05-1.15 (p=0.03) | 0.32 | 0.13-0.52 (p=0.001) | <0.001 | 85 |
| **NYHA functional class** |
| Up to II | 0 | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Up to III | 6 | [3, 4, 15, 18, 22, 24] | 0.37 | -0.14-0.88 (p=0.16) | 0.14 | -0.05-0.33 (p=0.15) | <0.001 | 85 |
| Up to IV | 3 | [16, 20, 21] | 0.32 | 0.07-0.57 (p=0.01) | 0.32 | 0.07-0.57 (p=0.01) | 0.60 | 0 |