Supplemental Digital Content 1. Risk of bias of included randomized studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| First Author | Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other bias |
| Dusing | Low | Some concerns | Low | Low | Some concerns | Low | Low |
| Noe | Low | Some concerns | Low | Some concerns | Some concerns | Low | Low |
| Murray | Low | Low | Low | Low | Low | Low | Low |
| Yamato | Low | Low | Low | Low | Low | Low | Low |
| Muller | Low | Low | Low | Low | Low | Low | Low |
| Lopez (2004) | Low | Low | Low | Low | Low | Low | Low |
| Kasama | Low | Low | Low | Unclear | Low | Low | Low |
| Lopez (2007) | Low | Low | Low | Low | Low | Low | Low |
| Torafic | Low | Low | Low | Low | Low | Low | Low |
| Trippel | Low | Low | Low | Low | Low | Low | Low |

**Supplemental Digital Content 2. Risk of bias of included observational studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| First Author | Bias due to confounding | Bias in participants selection | Bias due to departures from intended interventions | Bias in measurements of interventions | Bias due to missing data | Bias in selection of the reported result | Bias in measurement of outcomes |
| Spannherimer | Low | Low | Moderate | Low | Low | Low | Moderate |
| Cosin | Low | Low | Low | Low | Low | Low | Low |
| Mentz (PROTECT) | Low | Low | Low | Low | Low | Low | Low |
| Mentz (ASCEND-HF) | Low | Low | Low | Low | Low | Low | Low |

**Supplemental Digital Content 3. Baseline characteristics of 8,127 patients included in the quantitative analysis**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name** | **Age (mean)** | **Female (%)** | **NYHA 1 (%)** | **NYHA II (%)** | **NYHA III(%)** | **NYHA IV(%)** | **HTN**  **(%)** | **DM (%)** | **MI/**  **CAD (%)** | **CKD(%)** | **BB**  **(%)** | **ACEI/ARB (%)** | **MRA (%)** |
| **Dusing** | 69.5+9 | 55 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Noe** | 75.1 | 44 | NR | NR | NR | NR | 61 | 38 | 42 | NR | NR | NR | NR |
| **Spannheimer** | 69 | 57.5 | NR | 68.5 | 31.5 | NR | 52.5 | 24 | NR | 14.5 | NR | 46 | NR |
| **Murray** | 64.1 + 11.6 | 52.6 | NR | NR | NR | NR | 59.4 | 49.5 | 8.1/38.4 | 5.6 | 20.5 | 78.6 | 0.9 |
| **Cosin** | 68.5 + 11.0 | 50 | NR | 48 | 49.6 | NR | NR | NR | NR | NR | 9.5 | 30.8 | 3.3 |
| **Yamato** | 64.8 + 6.2 | 42 | NR | 34 | 66 | NR | 26 | NR | 50 | NR | 64 | 100 | NR |
| **Muller** | 73.8 +10.4 | 57 | NR | 55 | 42 | 3 | 29.1 | 75 | 46.4 | 86 | NR | NR | NR |
| **Lopez (2004)** | 63 +3 | 21.6 | NR | 36 | 56 | 8 | 58 | 0 | NR | NR | 100 | 100 | 0 |
| **Kasama** | 68 | 27.5 | NR | 37.5 | 62.5 | NR | NR | NR | NR | NR | 43.2 | 100 | 0 |
| **Lopez (2007)** | 63 +3.5 | 22.7 | 0 | 31.8 | 59.1 | 9.1 | 77 | NR | 22 | NR | 100 | 100 | NR |
| **TORAFIC** | 68.7 +10.6 | 41.9 | NR | 93 | 7 | NR | 100 | NR | NR | NR | 43 | 48.3 | 0 |
| **Mentz (ASCEND-HF)** | 69 (IQR 60-77) | 31 | NR | NR | 42.4 | 42 | 81.3 | 43.2 | NR | NR | 75.6 | 73.8 | 44.4 |
| **Mentz (PROTECT)** | 65 (IQR 54-75) | 34.3 | 2 | NR | 43.3 | 22.6 | 73 | 43.2 | 35.7/57.1 | NR | 59.1 | 59.3 | 0 |
| **Trippel** | 68.7+/-8.1 | 43 | 17 | NR | 37 | NR | 97 | 100 | 46 | NR | 63 | 46 | NR |

NYHA: New York Heart Association; HTN: hypertension; DM: diabetes mellitus; MI: myocardial infarction; CAD: coronary artery disease; CKD: chronic kidney disease; BB: beta blocker; ACE: angiotensin converting enzyme inhibitor; ARB: angiontensin receptor blocker; MRA: mineralocorticoid receptor antagonist