## Supplementary Material

## **Supplementary Table S1:** Search Strategy and Results

| Data Source | | | | Limits | | | | Duplicates Results | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Database | Vendor | Date searched | Database update | English only? | Time Period Searched | Publication types | Other Limits | Items found | Inner dups | Ext dups | New |
| Medline/PubMed | Ovid | 12/8/21 | - | No | No limit | No limit | - | 175 | 0 | 0 | 175 |
| Query: ((breast cancer) AND ((trastuzumab*) OR (pertuzumab))) AND ((prevention) AND (cardiotoxicity)) | | | | | | | | | | | |
| EMBASE | Elsevier | 12/8/21 | - | No | No limit | No limit | - | 703 | 6 | 25 | 672 |
| Query: (breast cancer.mp. or exp breast cancer/ AND (exp trastuzumab/ or trastuzumab.mp. OR exp pertuzumab/ or pertuzumab.mp.) AND (prevention.mp. or exp prevention/OR cardiotoxicity.mp. or exp cardiotoxicity/) | | | | | | | | | | | |
| Scopus | Elsevier | 12/8/21 | - | No | No limit | Article | - | 1653 | 2 | 105 | 1546 |
| Query: ( ( ( ALL ( "breast cancer" ) ) AND ( ALL ( "trastuzumab*" ) OR ALL ( "pertuzumab" ) ) ) AND ( ALL ( "prevention" ) AND ALL ( "cardiotoxicity" ) ) ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) ) | | | | | | | | | | | |
| Cochrane Library | Wiley | 12/8/21 | - | No | No limit | No limit | - | 54 | 2 | 20 | 32 |
| Query: "cardiotoxicity" AND "prevention" in All Text AND "breast cancer" AND ("trastuzumab" OR "pertuzumab") in All Text - (Word variations have been searched) | | | | | | | | | | | |

| | Items found | Inner dups | Ext dups | New |
|---|---|---|---|---|
| Totals | 2585 | 10 | 150 | 2425 |

## **Supplementary Table S2:** Summary of Findings Table

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With placebo | With heart failure therapies | | Risk with placebo | Risk difference with heart failure therapies |
| **Cardiotoxicity** | | | | | | | | | | | |
| 952 (3 RCTs) | not serious | serious[a] | not serious | serious[b] | none | ⨁⨁◯◯ Low | 120/471 (25.5%) | 110/481 (22.9%) | **RR 0.90** (0.63 to 1.29) | 255 per 1,000 | **25 fewer per 1,000** (from 94 fewer to 74 more) |
| **Follow-up LVEF** | | | | | | | | | | | |
| 466 (4 RCTs) | serious[c] | serious[a] | not serious | not serious | none | ⨁⨁◯◯ Low | 236 | 230 | - | The mean follow-up LVEF ranged from **54.5-59.3** % | MD **2.24 % higher** (0.53 higher to 3.94 higher) |
| **Trastuzumab interruption** | | | | | | | | | | | |
| 740 (2 RCTs) | not serious | not serious | not serious | not serious | none | ⨁⨁⨁⨁ High | 98/364 (26.9%) | 57/376 (15.2%) | **RR 0.57** (0.43 to 0.77) | 269 per 1,000 | **116 fewer per 1,000** (from 153 fewer to 62 fewer) |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

**Explanations**

a. Moderate unexplained heterogeneity
b. Confidence interval fails to exclude significant benefit or harm
c. Two included studies (Farahani et al. and Sherafati et al. ) had 'some concerns' on RoB2 assessment, in one domain each

## **Supplementary Table S3:** Risk of Bias Table

| Study ID | Experimental | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| Boekhoet 2016 | Candesartan | Placebo | Primary | 1 | + | + | + | + | + | + |
| Farahani 2019 | Carvedilol | No Therapy | Primary | 1 | + | ! | + | + | + | ! |
| Guglin 2019 | Carvidelol/Lisopril | Placebo | Primary | 1 | + | + | + | + | + | + |
| Pitushkin 2017 | Bisoprolol/Perindopril | Placebo | Primary | 1 | + | + | + | + | + | + |
| Sherafati 2018 | Carvedilol | No Therapy | Primary | 1 | + | + | + | + | ! | ! |

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result