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Table S1: Search strategy

|  |  |  |
| --- | --- | --- |
| **Database** | **Search terms** | **Results** |
| PubMed | (anthracycline or anthra\* or epirubicin or doxorubicin or daunorubicin or trastuzumab or herceptin) and (cardiac or cardiotox\* or cardiac dysfunction or lvef or ejection fraction or troponin or creatine kinase or natriuretic peptide or bnp or nt-bnp or stress or strain or systolic or diastolic) and (rct OR (random\* AND (control\*))) | 1,440 |
| EMBASE | ('anthracycline'/exp OR anthracycline OR anthra\* OR 'epirubicin'/exp OR epirubicin OR 'doxorubicin'/exp OR doxorubicin OR 'daunorubicin'/exp OR daunorubicin OR 'trastuzumab'/exp OR trastuzumab OR 'herceptin'/exp OR herceptin) AND ('cardiac'/exp OR cardiac OR cardiotox\* OR 'cardiac dysfunction'/exp OR 'cardiac dysfunction' OR (('cardiac'/exp OR cardiac) AND dysfunction) OR lvef OR 'ejection fraction'/exp OR 'ejection fraction' OR (ejection AND fraction) OR 'troponin'/exp OR troponin OR 'creatine kinase'/exp OR 'creatine kinase' OR (('creatine'/exp OR creatine) AND ('kinase'/exp OR kinase)) OR 'natriuretic peptide'/exp OR 'natriuretic peptide' OR (natriuretic AND ('peptide'/exp OR peptide)) OR bnp OR 'nt bnp' OR 'stress'/exp OR stress OR 'strain'/exp OR strain OR systolic OR diastolic) AND (rct OR (random\* AND control\*)) | 3,514 |
| CENTRAL | In all fields: (anthracycline or anthra\* or epirubicin or doxorubicin or daunorubicin or trastuzumab or herceptin) and (cardiac or cardiotox\* or cardiac dysfunction or lvef or ejection fraction or troponin or creatine kinase or natriuretic peptide or bnp or nt-bnp or stress or strain or systolic or diastolic) and (rct OR (random\* AND (control\*))) | 1,072 |

Table S2: Characteristics of included studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Year** | **n, patients** | **Gender (% male)** | **Mean age** | **Cancer** | **Anthracyclines** | **Baseline mean LVEF (%)** | **Duration of follow-up (Days)** |
| Lee | 2021 | 43 | 0 | 48.5 | Breast | Doxorubicin | 64 | 480 |
| Kaya | 2013 | 18 | 0 | 50.5 | Breast | Epirubicin | 66.6 | 480 |
| Avila | 2018 | 13 | 0 | 52.9 | Breast | NR | 65.2 | 180 |
| Bosch | 2013 | 37 | NR | 50 | Haematological cancers | NR | 62.59 | 630 |
| Boekhout | 2016 | 206 | 0 | 49 | Breast | NR | NR | 630 |
| Elitok | 2014 | 40 | 0 | 52.9 | Breast | NR | 65 | 180 |
| Nabati | 2017 | 40 | 0 | 47.1 | Breast | Doxorubicin | 61.13 | 180 |
| Acar | 2011 | 20 | 45 | 52.6 | Non-Hodgkin's lymphoma, multiple myeloma, leukemia | Doxorubicin or idarubicin | 62.9 | 180 |
| Kalay | 2006 | 25 | 16 | 49 | Breast, lymphomas | Doxorubicin or epirubicin | 69.7 | 180 |
| Georgakopoulos | 2010 | 40 | 53 | 49.1 | Lymphomas | Doxorubicin | 67.6 | 360 |
| Jhorawat | 2016 | 27 | 66.7 | 38.74 | Haematological cancers | Doxorubicin | 67.56 | 180 |
| Salehi | 2011 | 22 | 36.4 | 43.5 | Breast, lymphomas | Doxorubicin or epirubicin | 58.56 | 120 |
| Dessi | 2013 | 24 | 33.3 | 53 | Various | Epirubicin | 66 | 540 |
| Livi | 2021 | 42 | 0 | 48 | Breast | NR | 64.1 | 360 |
| Janbabai | 2016 | 35 | 11.4 | 47.06 | Various | Doxorubicin | 59.61 | 180 |
| Cardinale | 2006 | 58 | 33 | 44 | Breast, haematological cancers | NR | 61.8 | 270 |
| Abuosa | 2018 | 38 | 24 | 40.4 | Breast, lymphomas | Doxorubicin | 62 | 180 |
| Cochera | 2018 | 30 | 0 | 52 | Breast | Doxorubicin | 61 | 126 |
| Sun | 2015 | 40 | 0 | 55.11 | Breast | Epirubicin | 65 | 126 |
| Slowik | 2020 | 48 | 0 | 45 | Breast | NR | NR | 365 |
| Hundley | 2022 | 140 | 8 | 49.4 | Breast, lymphomas | Doxorubicin | 61.7 | 720 |
| Esfandbod | 2021 | 30 | 0 | 46.2 | Breast | Doxorubicin | 54.9 | 360 |
| Wihandono | 2021 | 25 | 0 | 50.8 | Breast | Doxorubicin | 65.64 | 150 |
| Farahani | 2019 | 35 | 0 | 57.4 | Breast | Doxorubicin or idarubicin | 54.93 | 90 |
| Cadeddu | 2010 | 24 | 0.33 | 53 | Various | Epirubicin | 66 | 28 |

Table S3: Subgroup analyses of cumulative decline in left ventricular ejection fraction (%) over time in cohorts of cancer patients receiving a cumulative anthracycline dose above 300 mg/m2 versus a cumulative anthracycline dose between 200 to 300 mg/m2. Abbreviations: k, number of studies; CI, confidence interval; n, number of patients.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Cohorts with CAD >300 mg/m2 | | | | | Cohorts with CAD 200-300 mg/m2 | | | | |
| Time (days) | k | Mean | Lower CI | Upper CI | n | k | Mean | Lower CI | Upper CI | n |
| 30 | 1 | 2 | 0.457 | 3.542 | 21 |  |  |  |  |  |
| 60 | 1 | 0 | -1.352 | 1.352 | 21 | 2 | -2.378 | -5.578 | 0.8217 | 56 |
| 90 | 2 | -3.799 | -11.247 | 3.648 | 79 | 2 | -2.335 | -5.633 | 0.9623 | 56 |
| 120 | 5 | -2.691 | -5.628 | 0.246 | 171 |  |  |  |  |  |
| 150 | 6 | -3.142 | -5.715 | -0.568 | 196 |  |  |  |  |  |
| 180 | 10 | -6.240 | -9.920 | -2.559 | 326 | 4 | -3.711 | -5.495 | -1.928 | 116 |
| 270 | 10 | -6.603 | -10.507 | -2.699 | 324 |  |  |  |  |  |
| 360 | 10 | -6.504 | -10.487 | -2.521 | 324 |  |  |  |  |  |
| 480 |  |  |  |  |  | 4 | -3.513 | -5.238 | -1.789 | 116 |
| 540 | 10 | -6.708 | -10.542 | -2.874 | 324 |  |  |  |  |  |
| 630 |  |  |  |  |  | 5 | -3.358 | -4.343 | -2.374 | 153 |

Table S4: Subgroup analyses of cumulative decline in left ventricular ejection fraction (%) over time in cohorts of cancer patients (A) with a baseline LVEF of 65 to 70% (B) with a baseline LVEF of 60 to 65%. Abbreviations: k, number of studies; CI, confidence interval; n, number of patients.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| A: Subgroup analysis of studies with baseline LVEF 65 to 70% | | | |  |  |
| Time (Days) | k | Mean | Lower CI | Upper CI | n |
| 30 | 2 | 0.949404762 | -1.008048981 | 2.906858505 | 45 |
| 60 | 3 | -0.250495486 | -0.99088429 | 0.489893319 | 58 |
| 90 | 3 | -0.196770938 | -0.954200274 | 0.560658397 | 58 |
| 150 | 4 | -1.415413053 | -3.883936479 | 1.053110373 | 83 |
| 180 | 6 | -5.052824098 | -10.29468464 | 0.189036445 | 126 |
| 360 | 7 | -4.310041025 | -8.959094917 | 0.339012866 | 166 |
| 480 | 8 | -4.908847329 | -9.102819917 | -0.714874741 | 184 |
| 540 | 8 | -5.161042087 | -9.180409349 | -1.141674825 | 184 |
| B: Subgroup analysis of studies with baseline LVEF 60 to 65% | | | |  |  |
| Time (Days) | k | Mean | Lower CI | Upper CI | n |
| 60 | 1 | -3.96666667 | -4.601371777 | -3.331961563 | 43 |
| 90 | 2 | -5.730447567 | -9.289539721 | -2.171355412 | 101 |
| 120 | 4 | -3.20508042 | -6.504861931 | 0.09470109 | 171 |
| 180 | 9 | -4.297650721 | -6.785509221 | -1.809792221 | 345 |
| 270 | 9 | -4.691378247 | -7.678009813 | -1.70474668 | 343 |
| 360 | 9 | -4.634908361 | -7.657462954 | -1.612353767 | 343 |
| 480 | 9 | -4.566757609 | -7.599097251 | -1.534417966 | 343 |
| 630 | 10 | -4.433753982 | -7.151800009 | -1.715707955 | 380 |
| 720 | 11 | -4.324949777 | -6.782451741 | -1.867447813 | 520 |

Table S5: Subgroup analyses of cumulative decline in left ventricular ejection fraction (%) over time in cohorts of cancer patients excluding studies with at least 10% of cancer patients receiving trastuzumab. Abbreviations: k, number of studies; CI, confidence interval; n, number of patients.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Analysis of LVEF excluding studies with >10% patients receiving trastuzumab | | | | |  |
| Time (Days) | k | Mean | Lower CI | Upper CI | n |
| 30 | 2 | 0.949404762 | -1.008048981 | 2.906858505 | 45 |
| 60 | 4 | -1.229147886 | -3.160625386 | 0.702329614 | 101 |
| 90 | 7 | -1.687277745 | -3.88180335 | 0.507247859 | 224 |
| 120 | 10 | -1.769694434 | -3.437833119 | -0.10155575 | 316 |
| 150 | 11 | -2.079387293 | -3.720336488 | -0.438438099 | 341 |
| 180 | 18 | -4.720534537 | -7.054574792 | -2.386494282 | 551 |
| 270 | 18 | -4.934523054 | -7.398575287 | -2.47047082 | 549 |
| 360 | 19 | -4.702005908 | -7.080384254 | -2.323627563 | 589 |
| 480 | 20 | -4.890950966 | -7.19181087 | -2.590091062 | 607 |
| 540 | 20 | -4.992631175 | -7.248651301 | -2.736611049 | 607 |
| 630 | 21 | -4.906991893 | -7.055323215 | -2.758660571 | 644 |
| 720 | 22 | -4.829087089 | -6.877905291 | -2.780268887 | 784 |

Table S6: Cumulative rise in natriuretic peptides (standardised mean) over time. Abbreviations: k, number of studies; CI, confidence interval; n, number of patients.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Time (days) | k | Mean change | Lower CI | Upper CI | n |
| 30 | 1 | 0 | -1.636 | 1.636 | 96 |
| 60 | 1 | 2 | -0.114 | 4.114 | 96 |
| 90 | 1 | -1 | -2.710 | 0.710 | 96 |
| 180 | 1 | -2 | -3.710 | -0.289 | 96 |
| 360 | 2 | 8.114 | -14.519 | 30.749 | 144 |
| 480 | 3 | 25.299 | -10.014 | 60.613 | 162 |
| 630 | 5 | 22.135 | 2.383 | 41.887 | 284 |

Figure S1: Risk of bias assessment.

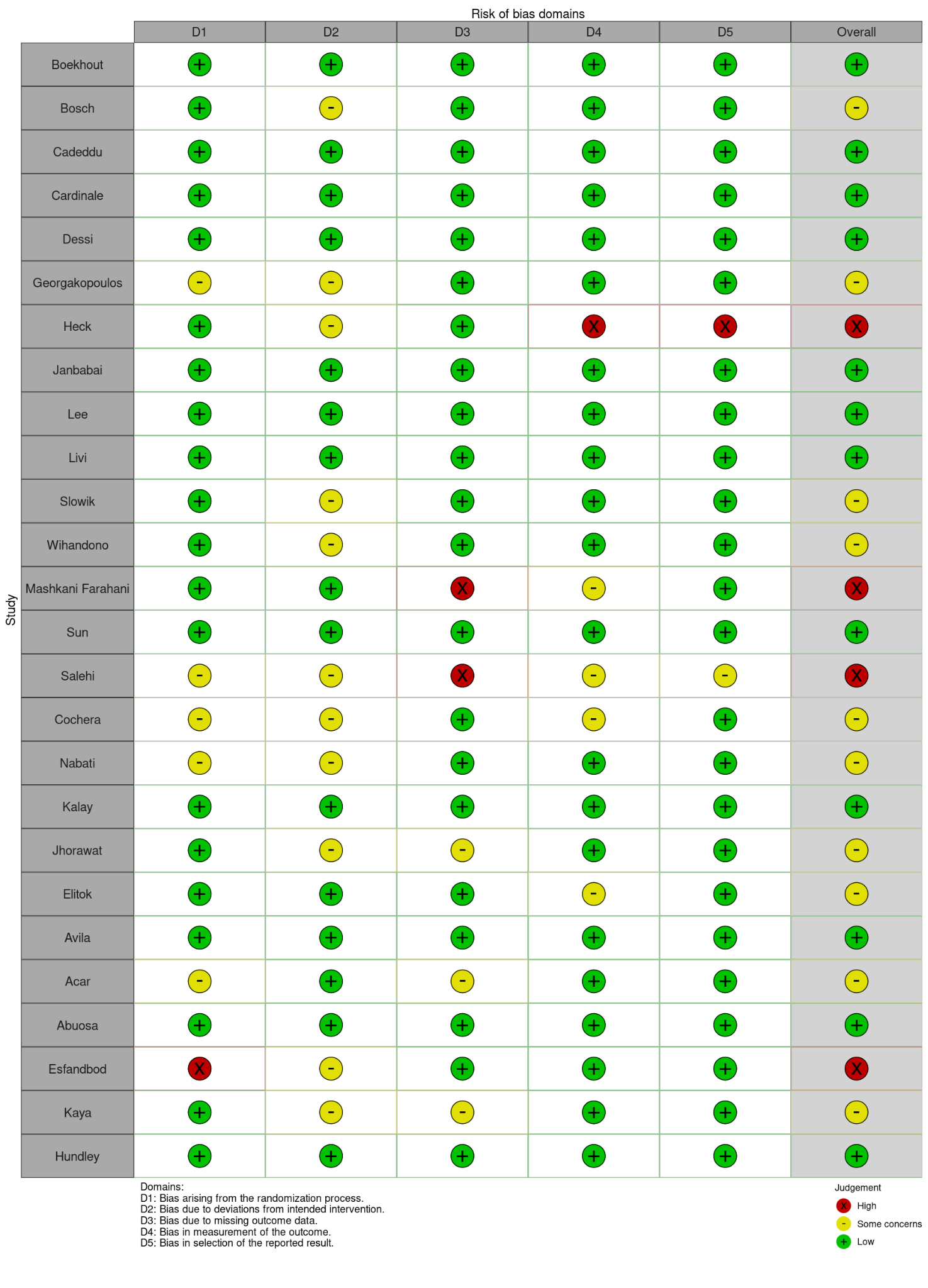


Figure S2: Cumulative rise in natriuretic peptides (standardised mean) over time. Whiskers represent 95% confidence intervals.

