**Supplementary materials**

**Search Strategy**

Medline, Embase and CENTRAL were searched using the following keywords:

- *heart failure* AND *normal ejection fraction*
- *heart failure* AND *preserved cardiac function*
- *heart failure* AND *preserved ejection fraction*
- *diastolic heart failure*
- *diastolic dysfunction*
- *HFpEF*
- *HFnEF*

Cochrane search filter for RCTs was applied

Source: (http://work.cochrane.org/rct-filters-different-databases)

| **Medline** | **EMBASE** | **Cochrane CENTRAL** |
|---|---|---|
| 1. Heart failure<br>2. Normal ejection fraction<br>3. Preserved cardiac function<br>4. Preserved ejection fraction<br>5. 1 and 2<br>6. 1 and 3<br>7. 1 and 4<br>8. Diastolic heart failure<br>9. Diastolic dysfunction<br>10. HFPEF<br>11. HFNEF<br>12. Or/5-11<br>13. Randomized Controlled Trials as Topic/<br>14. Randomized controlled trial/<br>15. Random Allocation/<br>16. Double Blind Method/<br>17. Single Blind Method/<br>18. Clinical trial/<br>19. Clinical trial, phase i.pt<br>20. Clinical trial, phase ii.pt<br>21. Clinical trial, phase | 1. Heart failure<br>2. Normal ejection fraction<br>3. Preserved cardiac function<br>4. Preserved ejection fraction<br>5. 1 and 2<br>6. 1 and 3<br>7. 1 and 4<br>8. Diastolic heart failure<br>9. Diastolic dysfunction<br>10. HFPEF<br>11. HFNEF<br>12. Or/5-11<br>13. Clinical trial/<br>14. Randomized controlled trial/<br>15. Randomization/<br>16. Single blind procedure/<br>17. Double blind procedure/<br>18. Crossover procedure/<br>19. Placebo/<br>20. Randomi?ed controlled trial$.tw.<br>21. Rct.tw.<br>22. Random allocation.tw. | In “Trials”<br>1. heart failure<br>2. preserved ejection fraction<br>3. preserved cardiac function<br>4. normal ejection fraction<br>5. 1 and 2<br>6. 1 and 3<br>7. 1 and 4<br>8. "diastolic heart failure"<br>9. "diastolic dysfunction"<br>10. "HFNEF"<br>11. "HFPEF"<br>12. 5 or 6 or 7 or 8 or 9 or 10 or 11 |

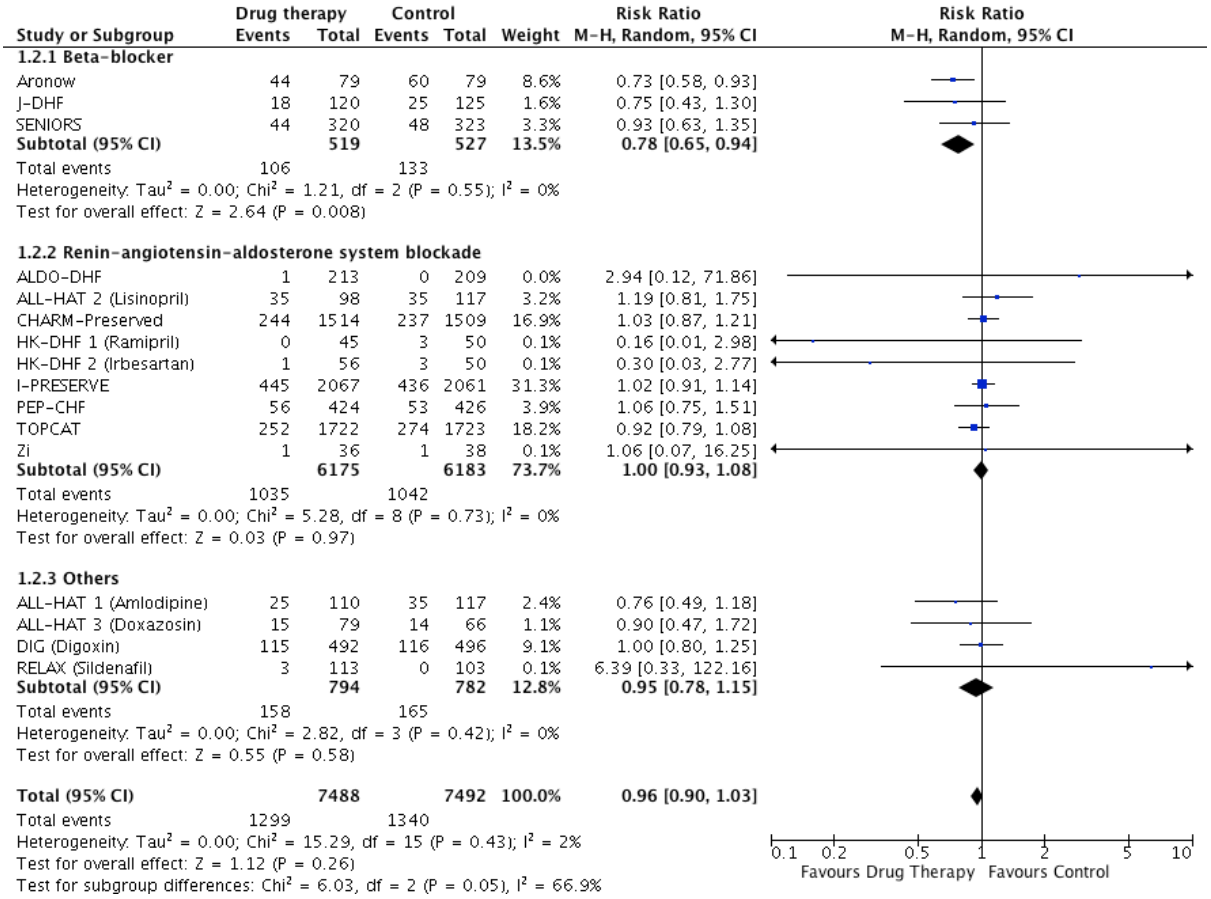
iii.pt
22. Clinical trial, phase iv.pt
23. Controlled clinical trial.pt
24. Randomized controlled trial.pt
25. Multicenter study.pt
26. Clinical trial.pt
27. Exp Clinical Trials as topic/
28. Or/13-27
29. (clinical adj trial$).tw
30. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw
31. Placebos/
32. Placebo$.tw
33. Randomly allocated.tw
34. (allocated adj2 random$).tw
35. Or/29-34
36. 28 or 35
37. Case report.tw
38. Letter/
39. Historical article/
40. Or/37-39
41. 36 not 40
42. 12 and 41

23. Randomly allocated.tw.
24. Allocated randomly.tw.
25. (allocated adj2 random).tw.
26. Single blind$.tw.
27. Double blind$.tw.
28. ((treble or triple) adj (blind$).tw.
29. Placebo$.tw.
30. Prospective study/
31. Or/13-30
32. Case study/
33. Case report.tw.
34. Abstract report/ or letter/
35. Or/32-34
36. 31 not 35
37. 12 and 36

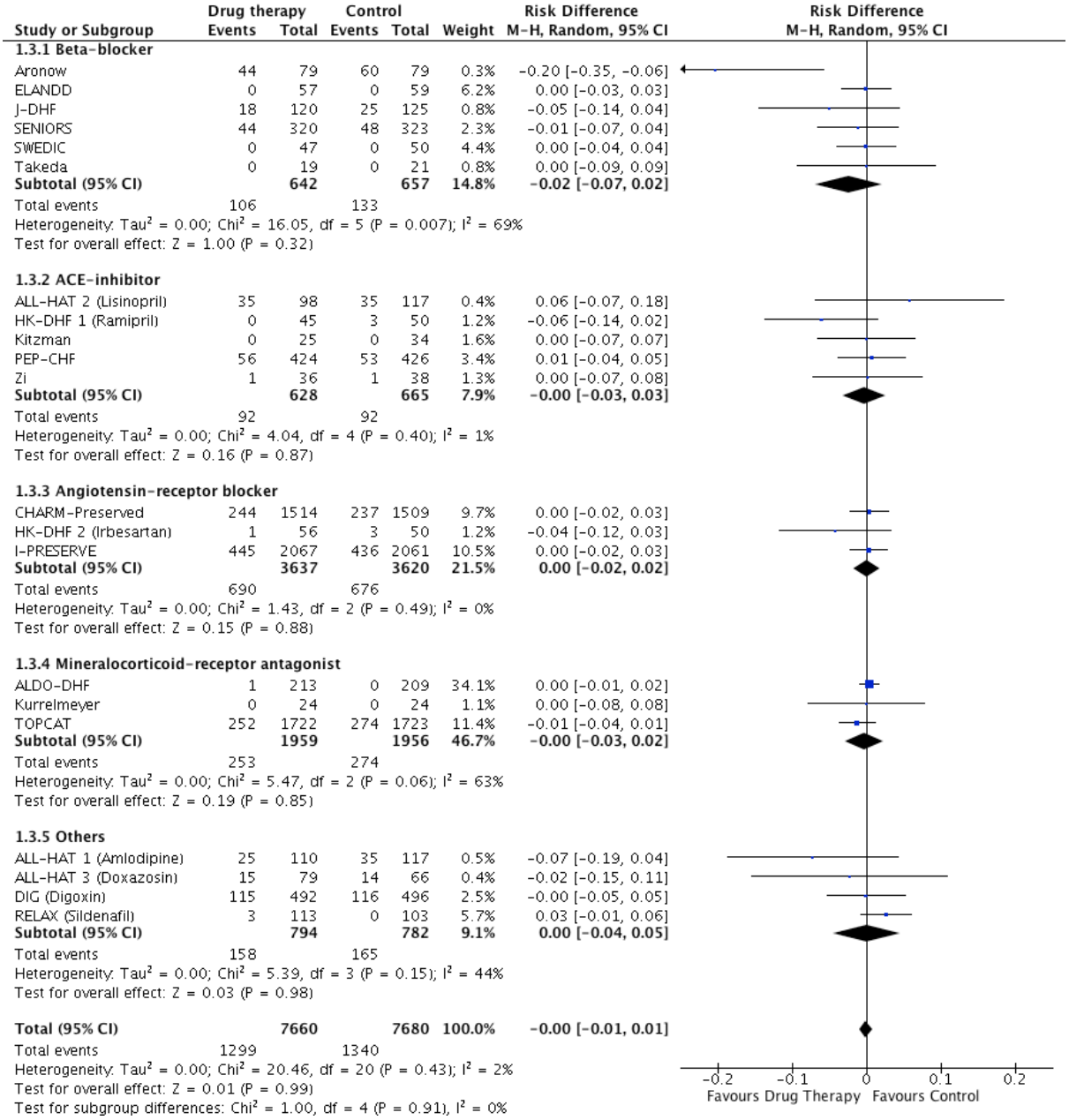
## Cochrane risk of bias assessment

| Author (Trial) | Selection bias | Performance bias | Detection bias | Reporting bias | Attrition bias | Overall risk of bias |
|---|---|---|---|---|---|---|
| Ahmed (DIG) | Low | Low | Low | Low | Low | Low |
| Aronow | Unclear | High | Low | Low | Low | High |
| Bergstrom (SWEDIC) | Unclear | Low | Low | Low | Low | Low |
| Cleland (PEP-CHF) | Low | Low | Low | Low | Unclear | Low |
| Conraads | Low | Low | Low | Low | Low | Low |
| Davis (ALLHAT) | Unclear | Low | Low | Low | Low | Low |
| Deswal (RAAM-PEF) | Unclear | Low | Low | Low | Low | Low |
| Edelmann (ALDO-DHF) | Low | Low | Low | Low | Low | Low |
| Hung | Low | Low | Low | Low | Low | Low |
| Kasama | Low | Low | Low | Low | Low | Low |
| Kitzman | Low | Low | Low | Low | Low | Low |
| Kurrelmeyer | Low | Low | Low | Low | Low | Low |
| Little | Low | Low | Low | Low | Low | Low |
| Mak | Low | High | Low | Low | Low | High |
| Massie (I-PRESERVE) | Low | Low | Low | Low | Low | Low |
| Parthasarathy | Low | Low | Low | Low | Low | Low |
| Pitt (TOPCAT) | Low | Low | Low | Low | Low | Low |
| Rector (I-PRESERVE) | Low | Low | Low | Low | Low | Low |
| Redfield (RELAX) | Low | Low | Low | Low | Low | Low |
| Takeda | Unclear | High | Unclear | Low | Low | High |
| Van Veldhuisen (SENIORS) | Low | Low | Low | Low | Low | Low |
| Yamamoto (J-DHF) | Unclear | High | Low | Low | Low | High |
| Yip (HK-DHF) | Low | High | Low | Low | Unclear | High |
| Yusuf (CHARM-preserved) | Low | Low | Low | Low | Low | Low |
| Zi | Unclear | Low | Low | Low | Low | Low |
| Zile | Unclear | Low | Low | Low | Low | Low |

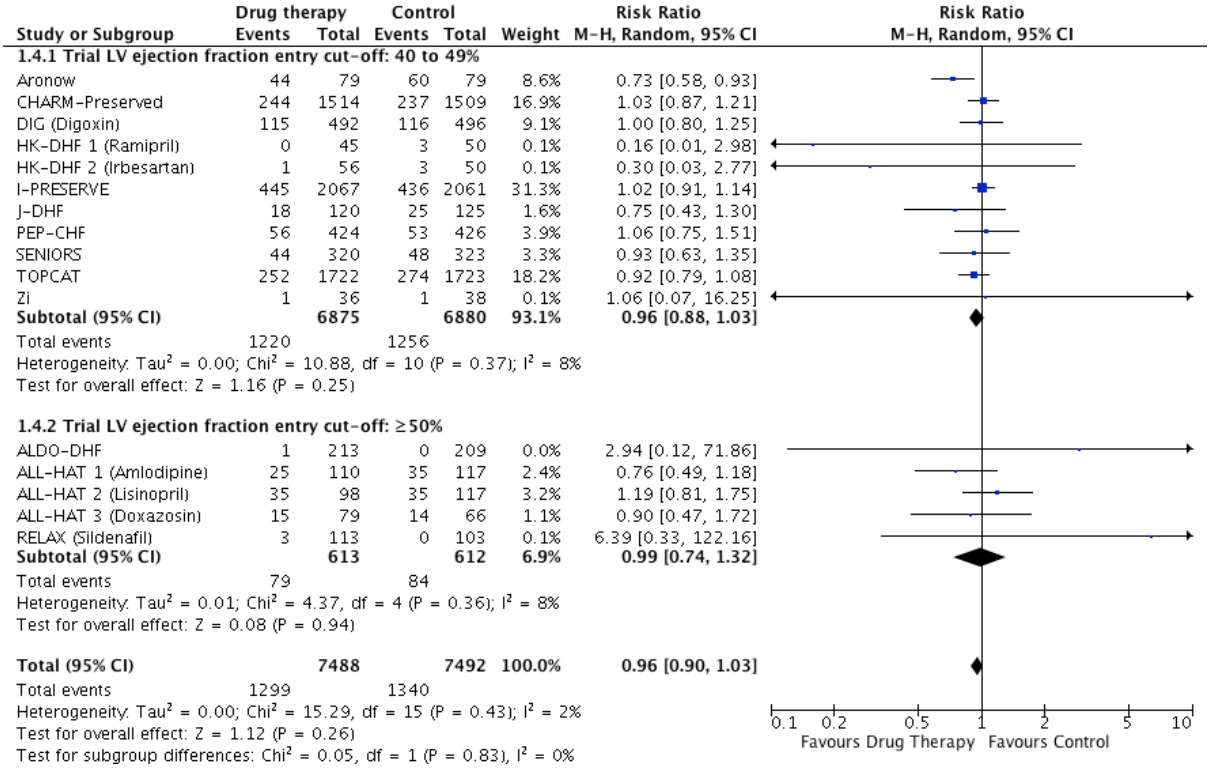
**Supplementary Figure 1A**: Pooled and individual estimates of relative risk (RR) and 95% confidence intervals (CI) of the primary outcome all cause-mortality for different drug classes. Data is shown stratified by beta-blockers, renin-angiotensin-aldosterone antagonists (RAAS) [which includes Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARB), and Mineralocorticoid Receptor Antagonists(MRA)], and other drug classes. Random effects model used.



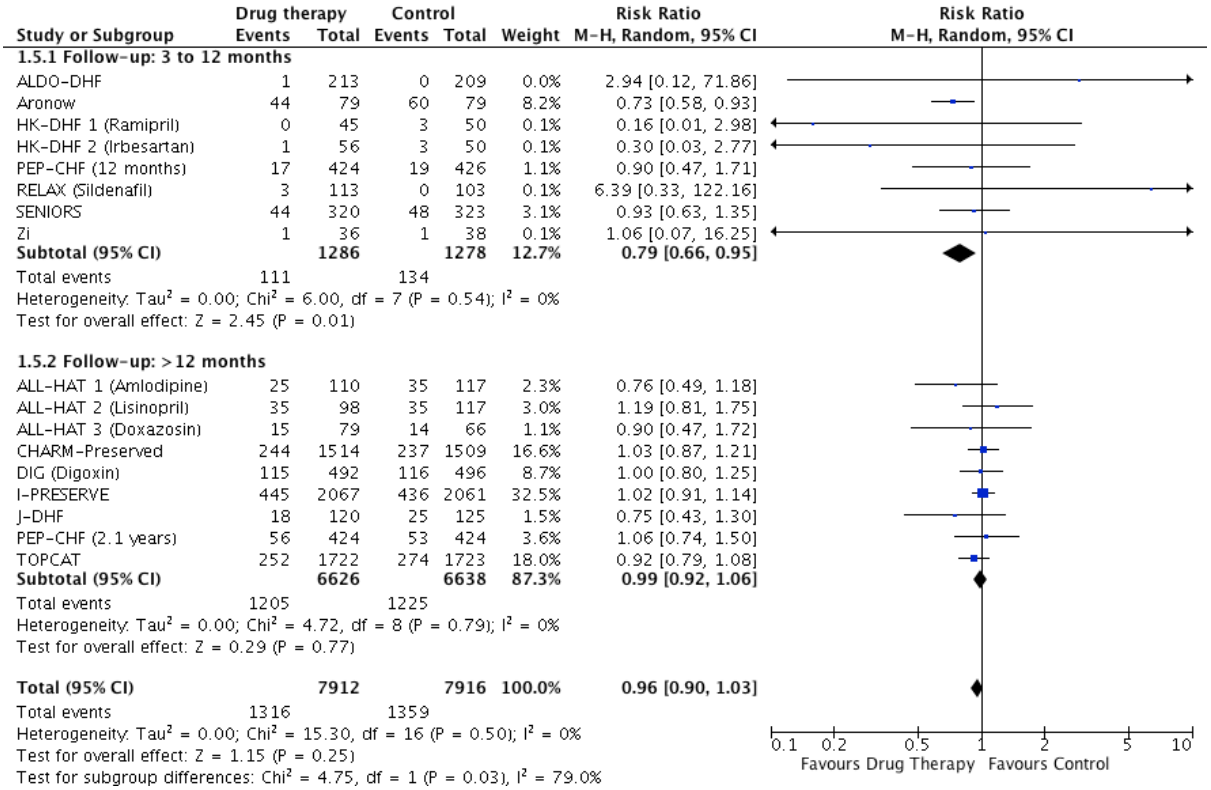
**Supplementary Figure 1B**: Pooled and individual estimates of risk difference (RD) and 95% CI of the primary outcome all cause-mortality for different drug classes. Data is shown stratified by beta-blockers, ACE inhibitors, ARB, and MRA, and other drug classes. Random effects model used.



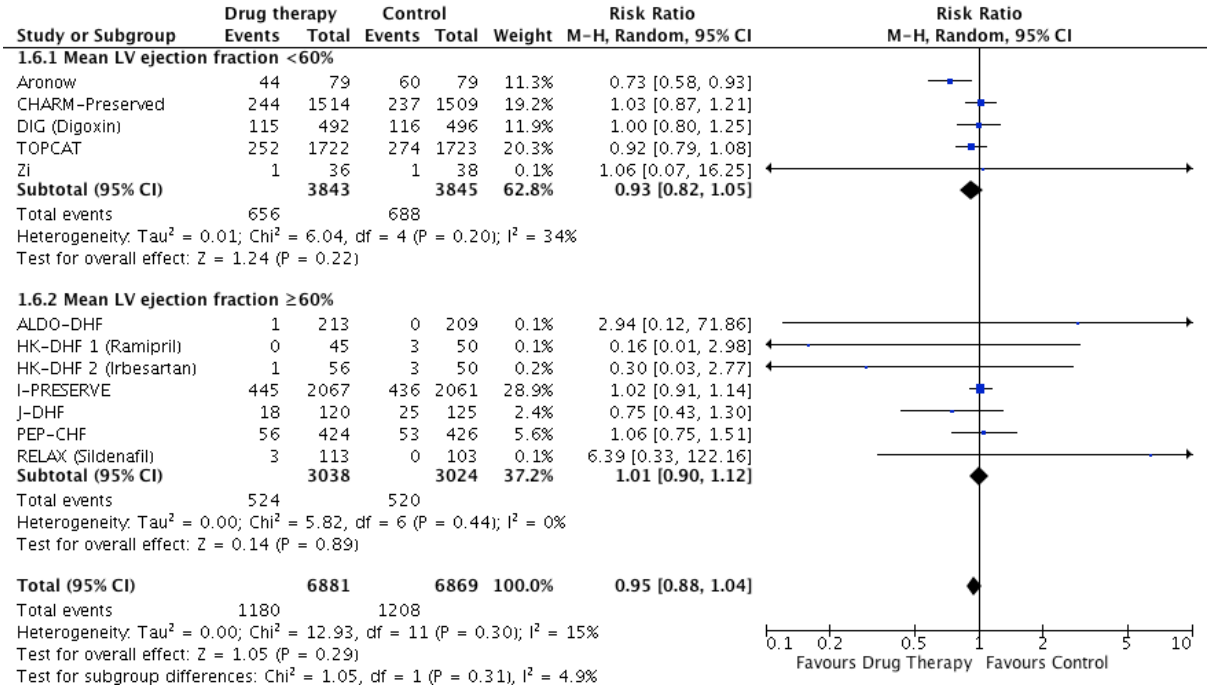
**Supplementary Figure 1C**: Pooled and individual estimates of relative risk (RR) and 95% CI of the primary outcome all cause-mortality stratified by entry LV ejection fraction threshold: 40 to 49% (trials which include patients with HFmrEF), and ≥50% (trials which include only HFpEF). Random effects model used.



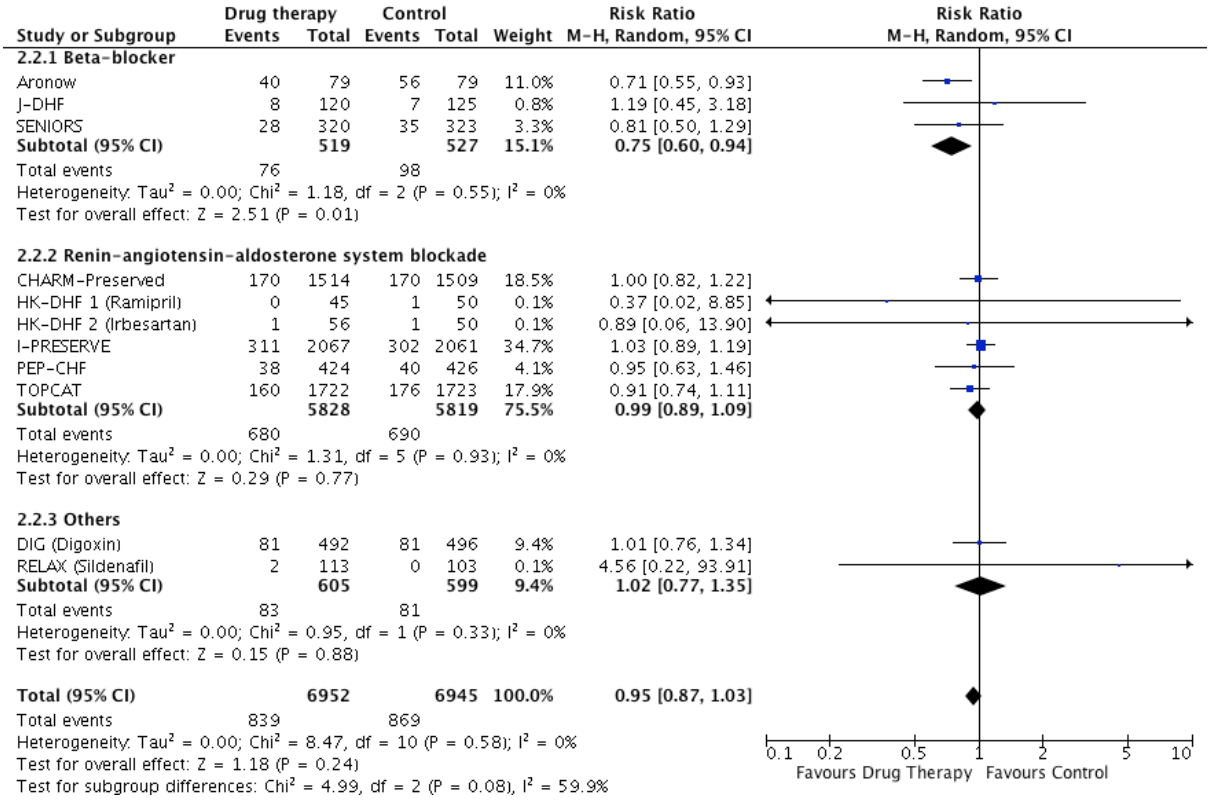
**Supplementary Figure 1D**: Pooled and individual estimates of relative risk (RR) and 95% CI of the primary outcome all cause-mortality stratified by follow-up duration: between 3 to 12 months and greater than 12 months. Random effects model used. PEP-CHF reported outcomes at 12 months follow-up in addition to end of follow-up (mean 2.1 years).



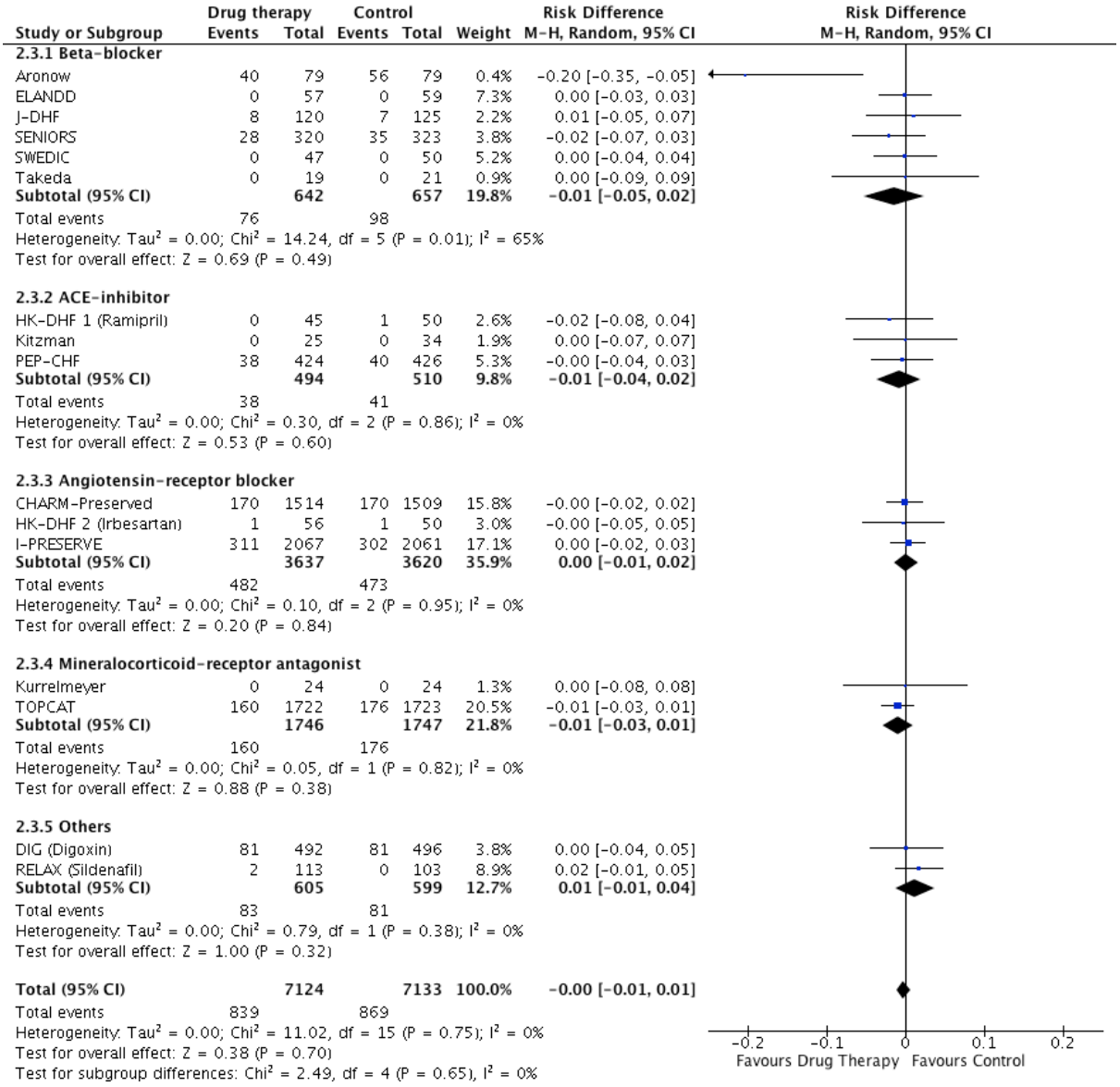
**Supplementary Figure 1E**: Pooled and individual estimates of relative risk (RR) and 95% CI of the primary outcome all cause-mortality stratified by mean LV ejection fraction: <60% and ≥60%. Random effects model used.



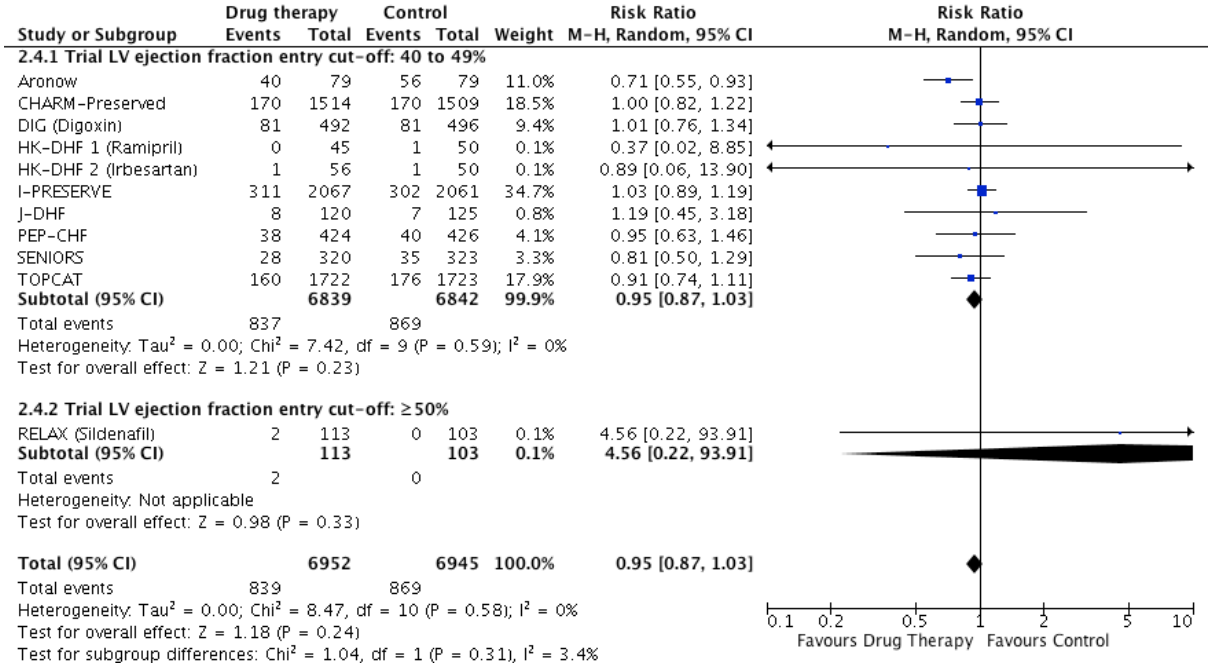
**Supplementary Figure 2A**: Pooled and individual estimates of relative risk (RR) and 95% CI of the cardiovascular mortality for different drug classes. Data is shown stratified by beta-blockers, RAAS antagonists (which includes ACE inhibitors, ARB, and MRA), and other drug classes. Random effects model used.



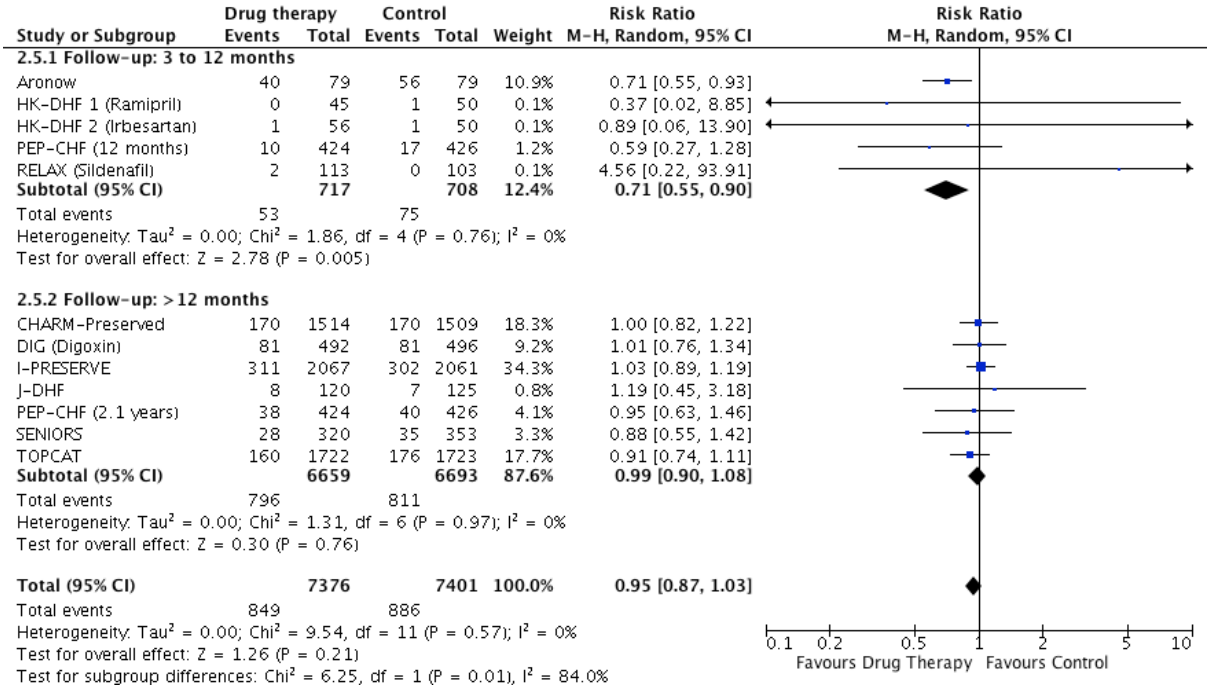
**Supplementary Figure 2B**: Pooled and individual estimates of risk difference (RD) and 95% CI of cardiovascular mortality for different drug classes. Data is shown stratified by beta-blockers, ACE inhibitors, ARB, and MRA, and other drug classes. Random effects model used.



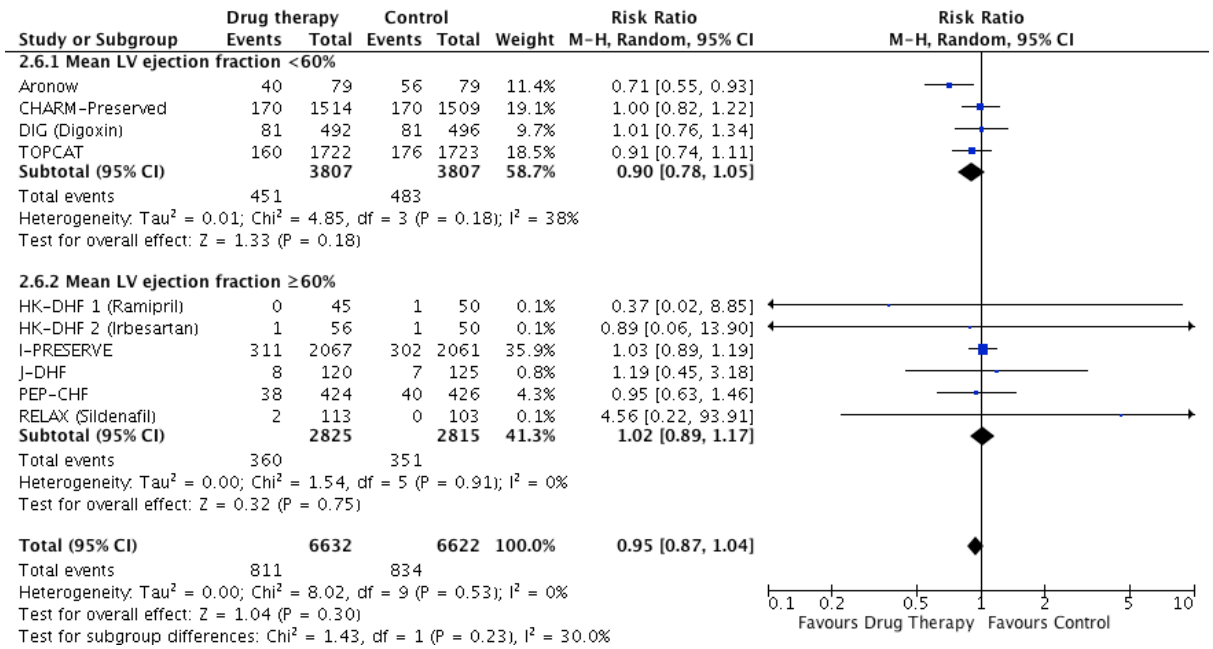
**Supplementary Figure 2C**: Pooled and individual estimates of relative risk (RR) and 95% CI of cardiovascular mortality stratified by entry LV ejection fraction threshold: 40 to 49% (trials which include patients with HFmrEF), and ≥50% (trials which include only HFpEF). Random effects model used. Only one trial (RELAX) using an LV ejection fraction threshold of 50% reported cardiovascular mortality.



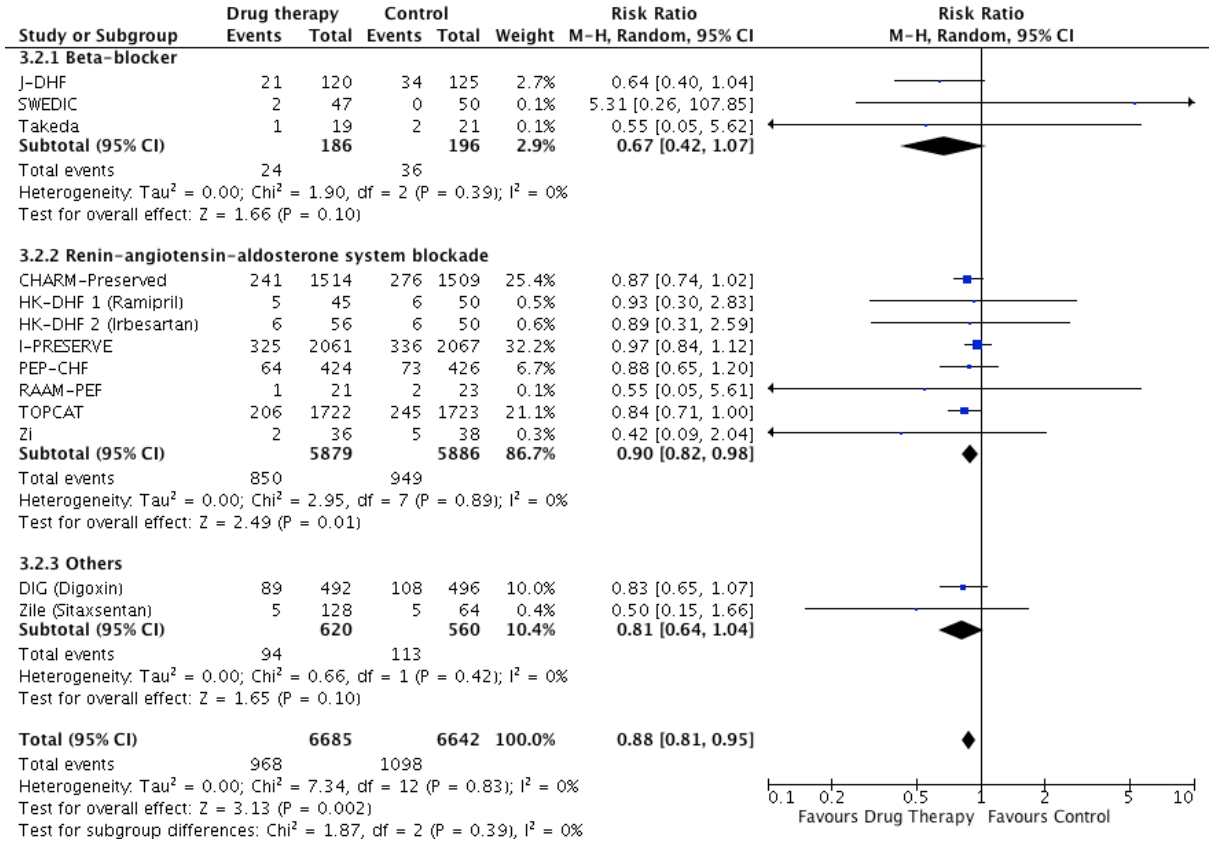
**Supplementary Figure 2D**: Pooled and individual estimates of relative risk (RR) and 95% CI of cardiovascular mortality stratified by follow-up duration: between 3 to 12 months and greater than 12 months. Random effects model used. PEP-CHF reported outcomes at 12 months follow-up in addition to end of follow-up (mean 2.1 years).



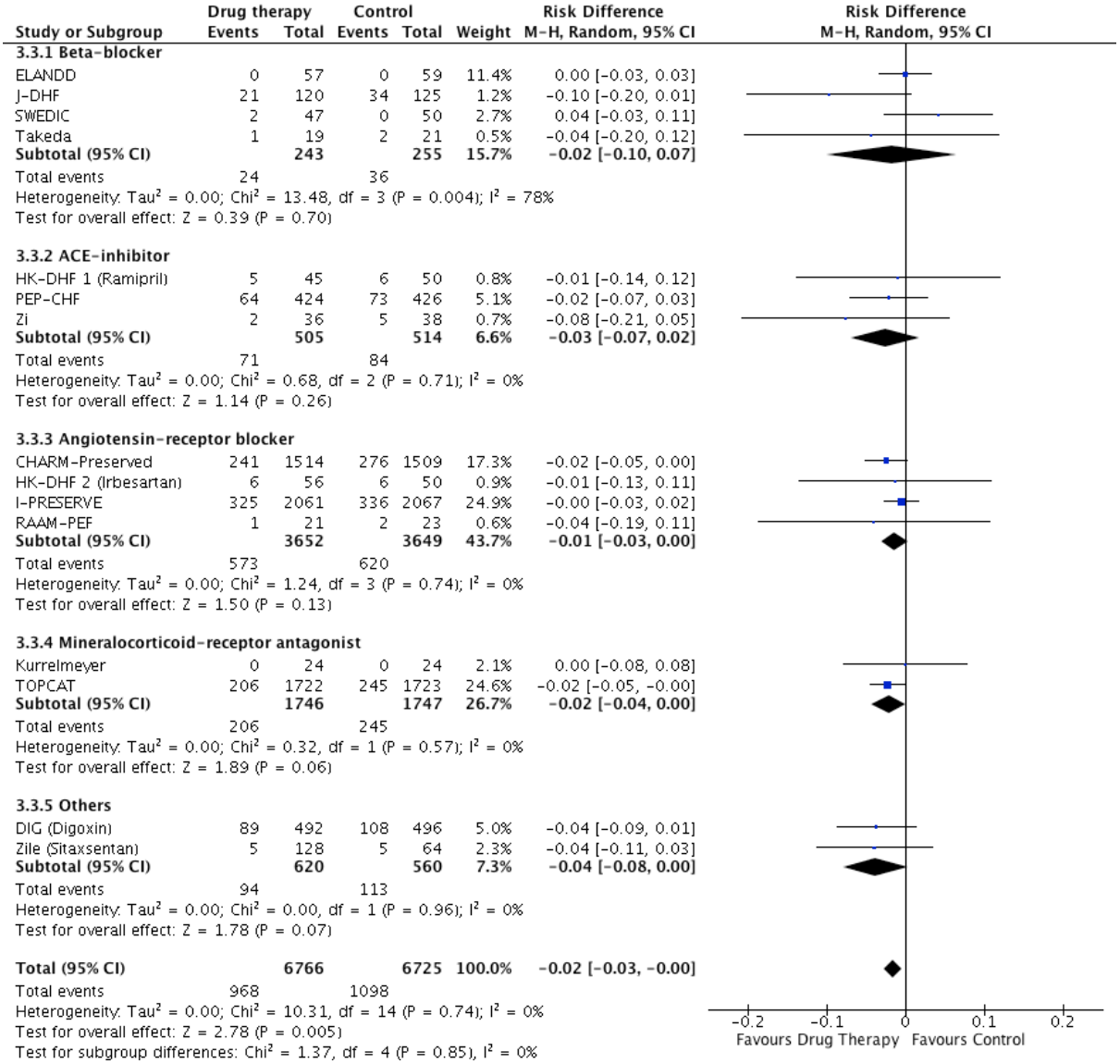
**Supplementary Figure 2E:** Pooled and individual estimates of relative risk (RR) and 95% CI of cardiovascular mortality stratified by mean LV ejection fraction: <60% and ≥60%. Random effects model used.



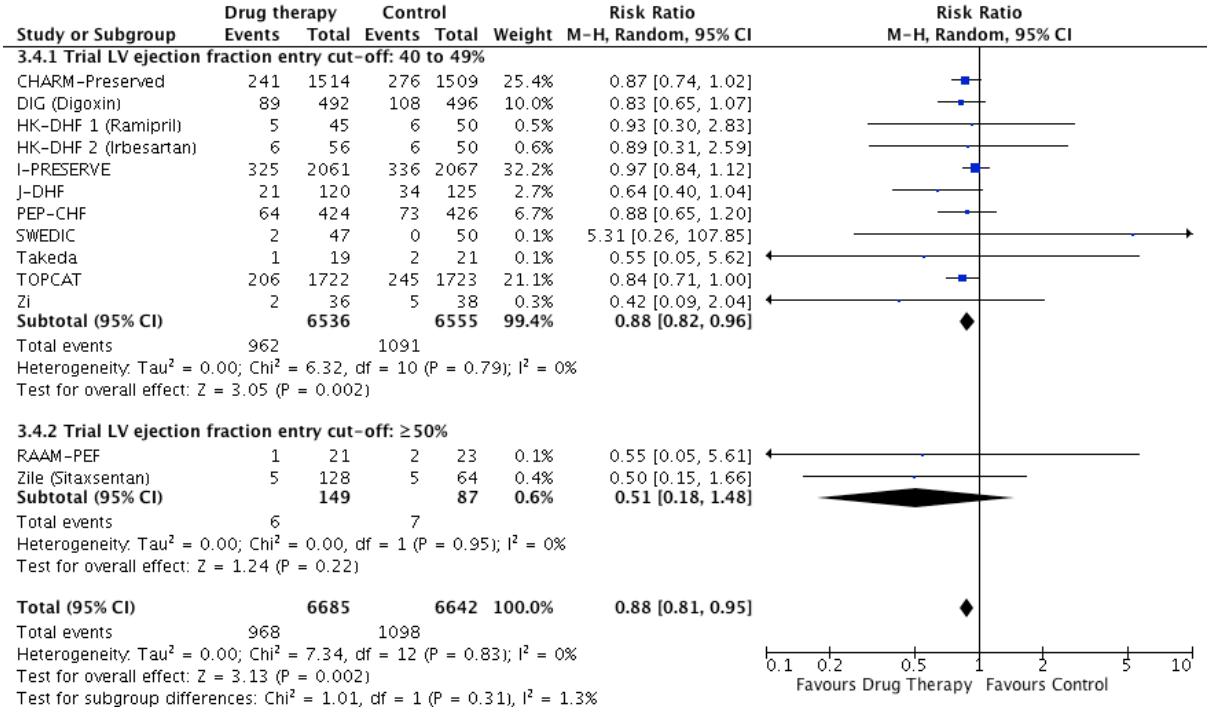
**Supplementary Figure 3A**: Pooled and individual estimates of relative risk (RR) and 95% CI of heart failure hospitalisation for different drug classes. Data is shown stratified by beta-blockers, RAAS antagonists (which includes ACE inhibitors, ARB, and MRA), and other drug classes. Random effects model used.



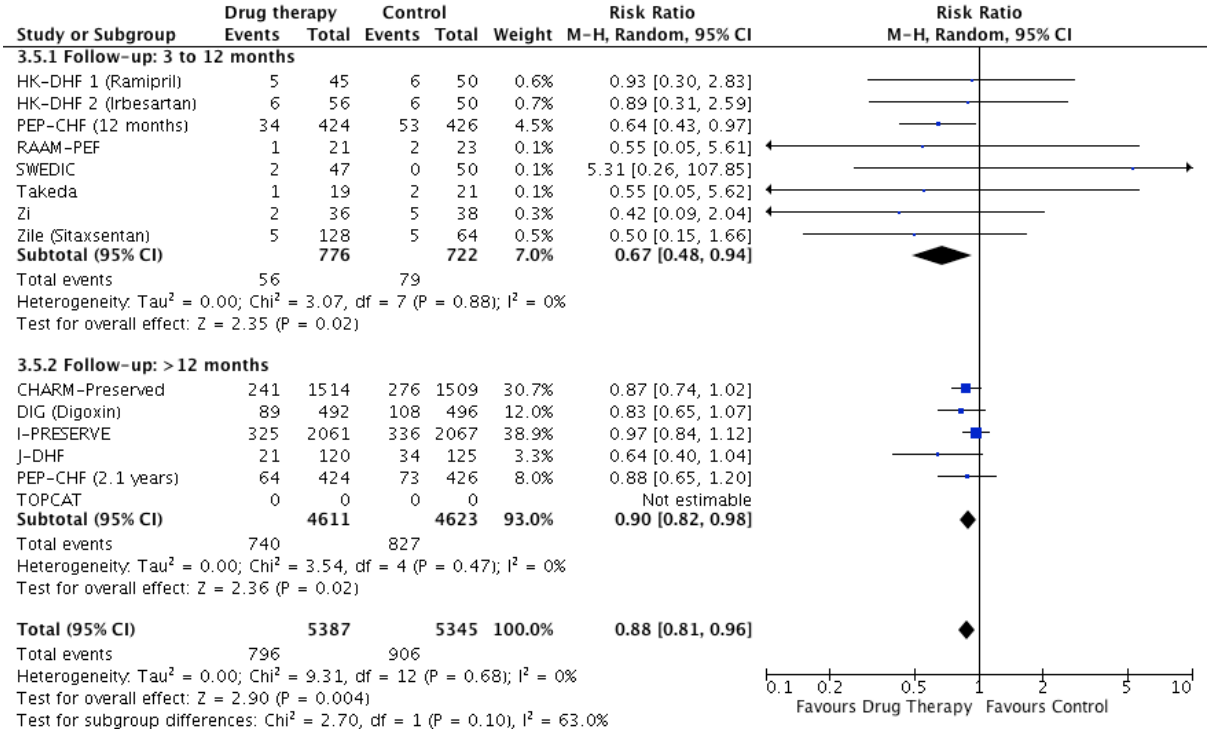
**Supplementary Figure 3B**: Pooled and individual estimates of risk difference (RD) and 95% CI of heart failure hospitalisation for different drug classes. Data is shown stratified by beta-blockers, ACE inhibitors, ARB, and MRA, and other drug classes. Random effects model used.



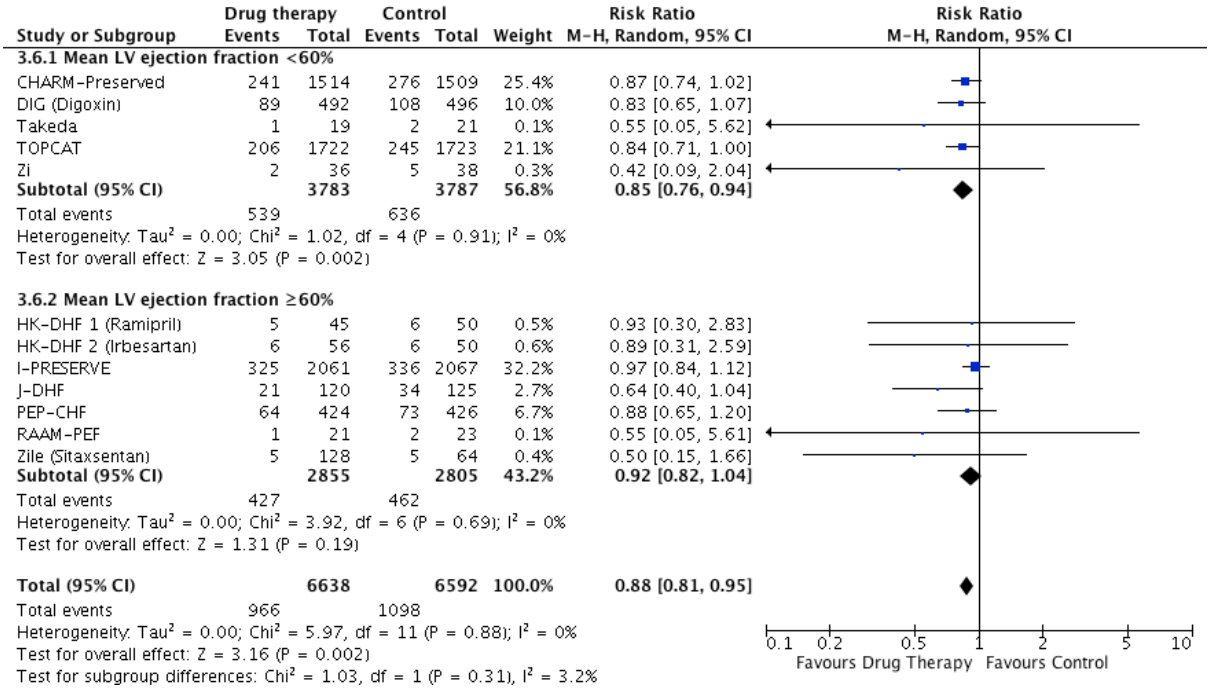
**Supplementary Figure 3C**: Pooled and individual estimates of relative risk (RR) and 95% CI of heart failure hospitalisation stratified by entry LV ejection fraction threshold: 40 to 49% (trials which include patients with HFmrEF), and ≥50% (trials which include only HFpEF). Random effects model used.



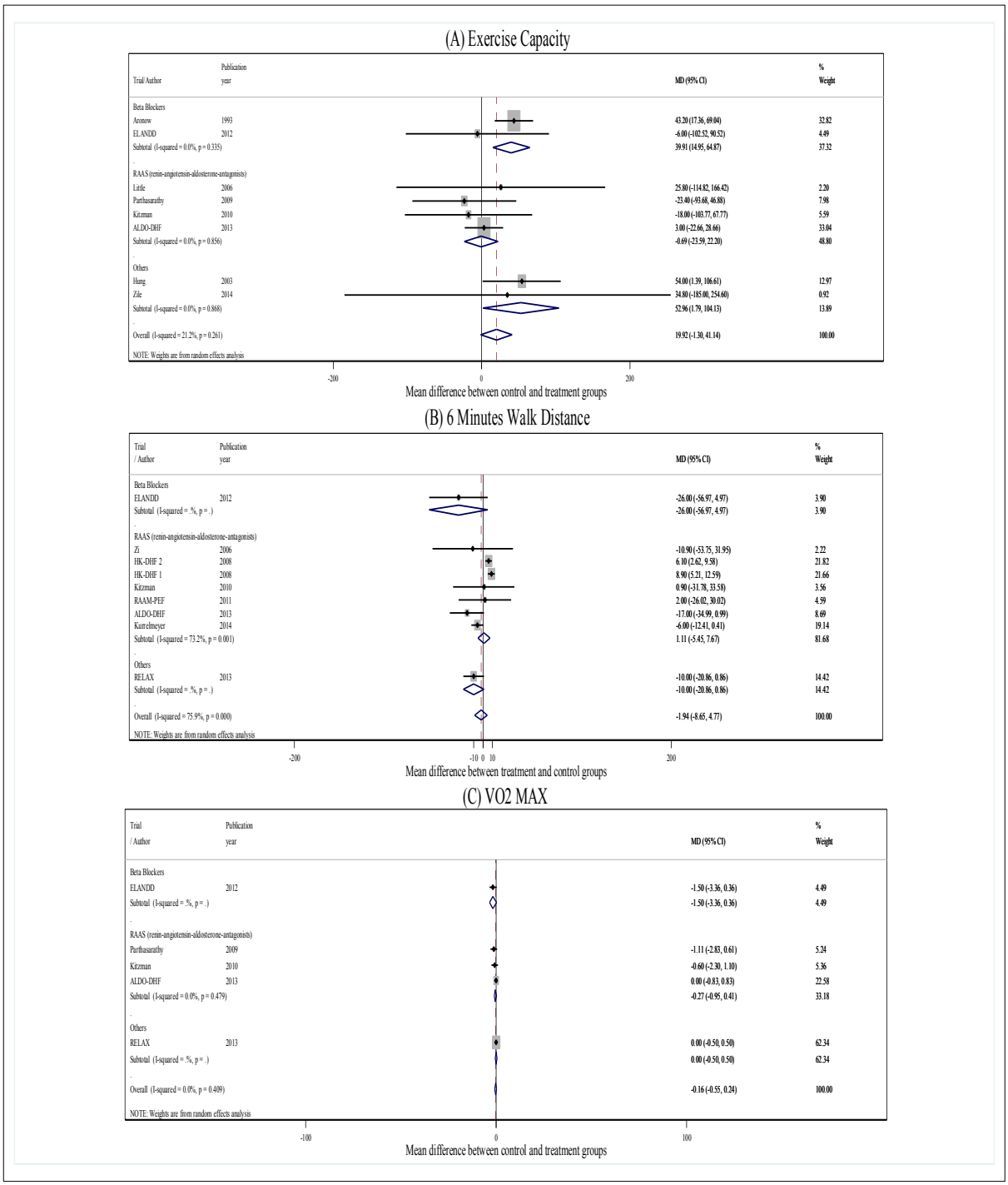
**Supplementary Figure 3D**: Pooled and individual estimates of relative risk (RR) and 95% CI of heart failure hospitalisation stratified by follow-up duration: between 3 to 12 months and greater than 12 months. Random effects model used. PEP-CHF reported outcomes at 12 months follow-up in addition to end of follow-up (mean 2.1 years).



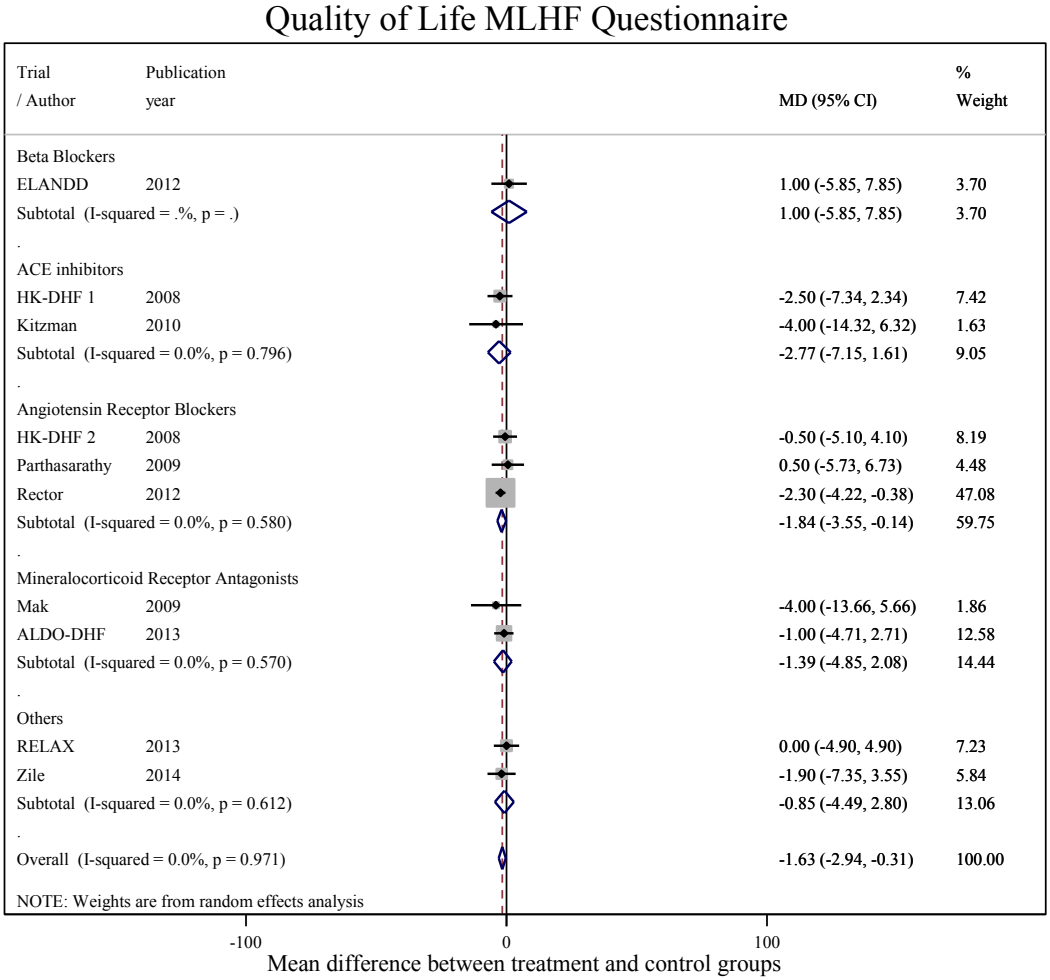
**Supplementary Figure 3E**: Pooled and individual estimates of relative risk (RR) and 95% CI of heart failure hospitalisation stratified by mean LV ejection fraction: <60% and ≥60%. Random effects model used.



**Supplementary Figure 4:** Pooled and individual estimates of standardised mean difference (MD) in exercise outcomes: (A) exercise capacity, (B) 6 minutes' walk distance, and (C) $VO_2$ max. Estimates and 95% CI based on a random effects model. Studies were stratified by individual drug classes (beta-blockers, renin-angiotensin-aldosterone system antagonists and other drug classes). Due to small number of studies, no classification was made by individual drug class blockers. RAAS includes Angiotensin Converting Enzyme inhibitors, Angiotensin Receptor Blockers and Mineralocorticoid Receptor Antagonist.

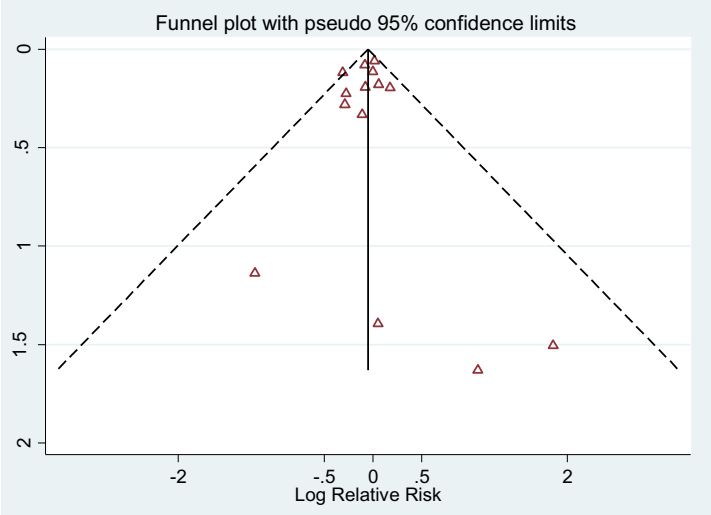


**Supplementary Figure 5**: Pooled and individual estimates of the standardised mean difference (MD) in quality of life, assessed by Minnesota Living with Heart Failure Questionnaire (MLHFQ). Lower MLHFQ scores associated with reduced symptoms, therefore; negative difference indicates improvement. Data is shown stratified by individual drug classes (beta-blockers, ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and other drug classes). Estimates and 95% CI were based on a random effects model.

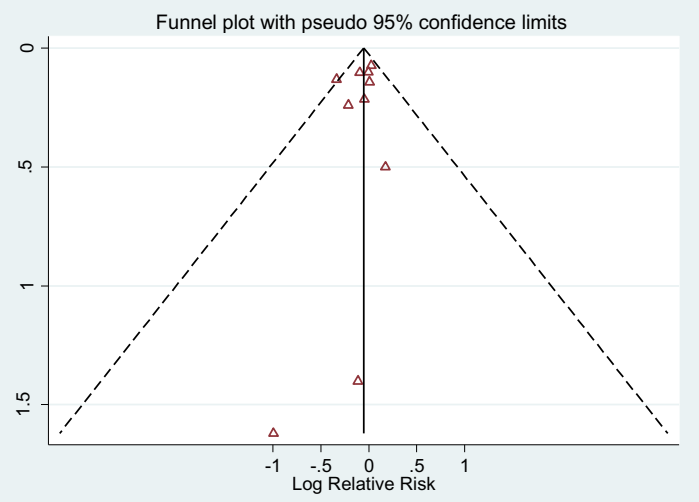


**Supplementary Figure 6** – Funnel plot

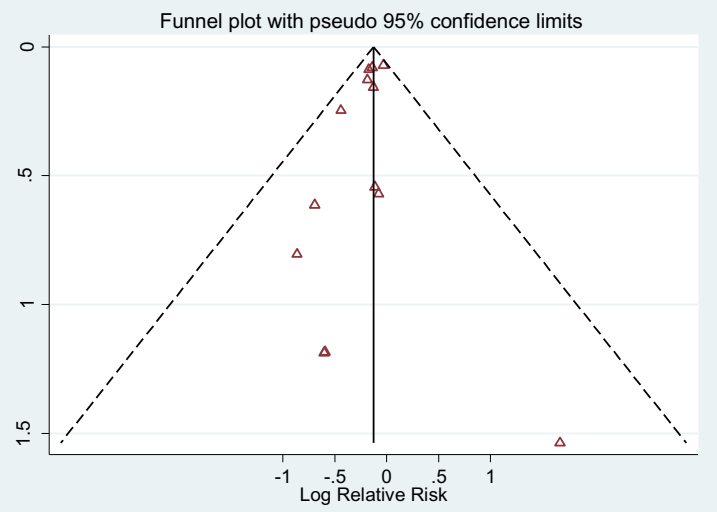
Supplementary Figure 6A: All-cause mortality




Supplementary Figure 6B: Cardiovascular mortality




Supplementary Figure 6C: Heart failure hospitalisation



**Supplementary Table 1**: Study characteristics for randomized controlled trials

| Author (Trial) | Arm | Year | Intervention | Control | Entry-EF cut-off | Follow-up (months) | Intervention (N) | Control (N) | Total (N) | Mean LVEF | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ahmed (DIG)**[1] | | 2005 | Digoxin | Placebo | 45% | 37 | 492 | 496 | 988 | 55 | All-cause mortality, CV mortality, HFH |
| **Aronow**[2] | | 1997 | Propranolol | No treatment | 40% | 12 | 79 | 79 | 158 | 57 | All-cause mortality, CV mortality, |
| **Bergstrom (SWEDIC)**[3] | | 2004 | Carvedilol | Placebo | 45% | 6 | 47 | 50 | 97 | NR | HFH, biomarker |
| **Cleland (PEP-CHF)**[4] | | 2006 | Perindopril | Placebo | 40% | 25.2 | 424 | 426 | 850 | 65 | All-cause mortality, CV mortality, HFH, exercise time, biomarker |
| **Conraads**[5] | | 2012 | Nebivolol | Placebo | 45% | 6 | 57 | 59 | 116 | 63 | 6MWD, $VO_2$, QOL, biomarker |
| **Davis (ALLHAT)**[6] | 1 | 2008 | Amlodipine | Chlorthalidone | 50% | 20.9 | 110 | 117 | 227 | NR | All-cause mortality |
| **Davis (ALLHAT)** | 2 | 2008 | Lisinopril | Chlorthalidone | | 20.9 | 98 | | 215 | NR | |
| **Davis (ALLHAT)** | 3 | 2008 | Doxazosin | Chlorthalidone | | 18.6 | 79 | 66 | 145 | NR | |
| **Deswal (RAAM-PEF)**[7] | | 2011 | Eplenerone | Placebo | 50% | 6 | 22 | 22 | 44 | 62 | HFH, 6MWD |
| **Edelmann (ALDO-DHF)**[8] | | 2013 | Spironolactone | Placebo | 50% | 12 | 213 | 209 | 422 | 67 | All-cause mortality, exercise time, 6MWD, $VO_2$, QOL, biomarker |
| **Hung**[9] | | 2003 | Verapamil | Placebo | 50% | 3 | 15 | 15 | 15 | 70 | Exercise time |
| **Kasama**[10] | | 2005 | Candesartan | Placebo | 40% | 6 | 25 | 25 | 50 | 55 | Biomarker |
| **Kitzman**[11] | | 2010 | Enalapril | Placebo | 50% | 12 | 35 | 36 | 71 | 65 | Exercise time, 6MWD, $VO_2$, QOL, biomarker |
| **Kurrelmeyer**[12] | | 2014 | Spironolactone | Placebo | 50% | 6 | 24 | 24 | 48 | 63 | 6MWD, Biomarker |
| **Little**[13] | | 2006 | Losartan | Hydrochlorothiazide | 50% | 6 | 19 | 21 | 40 | 67 | Exercise time, $VO_2$, |
| **Mak**[14] | | 2009 | Epleronone | Placebo | 45% | 12 | 24 | 20 | 44 | 63 | QOL, biomarker |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Massie (I-PRESERVE)[15]** | | 2008 | Irbesartan | Placebo | 45% | 49.5 | 2067 | 2061 | 4128 | 60 | All-cause mortality, CV mortality, HFH, QOL, biomarker |
| **Parthasarathy[16]** | | 2009 | Valsartan | Placebo | 40% | 3.5 | 70 | 82 | 152 | 71 | Exercise time, 6MWD, $VO_2$, QOL, biomarker |
| **Pitt (TOPCAT)[17]** | | 2014 | Spironolactone | Placebo | 45% | 49.5 | 1722 | 1723 | 3445 | 56 | All-cause mortality, CV mortality, HFH |
| **Rector (I-PRESERVE)[18]** | | 2012 | Irbesartan | Placebo | 45% | 56 | 1102 | 1103 | 2205 | NR | QOL |
| **Redfield (RELAX)[19]** | | 2013 | Sildenafil | Placebo | 50% | 6 | 113 | 103 | 216 | 60 | All-cause mortality, 6MWD, $VO_2$, QOL, biomarker |
| **Solomon (CHARM-Preserved)[20]** | | 2004 | Candesartan | Placebo | 40% | 36.6 | 1514 | 1509 | 3023 | 54 | All-cause mortality |
| **Takeda[21]** | | 2004 | Carvedilol | No treatment | 45% | 12 | 19 | 21 | 40 | 57 | HFH, QOL, biomarker |
| **Van Veldhuisen (SENIORS)[22]** | | 2009 | Nebivolol | Placebo | 35% | 21 | 320 | 323 | 643 | NA | All-cause mortality, CV mortality |
| **Yamamoto (J-DHF)[23]** | | 2013 | Carvedilol | Placebo | 40% | 38.4 | 120 | 125 | 245 | 63 | All-cause mortality, CV mortality, HFH |
| **Yip (HK-DHF)[24]** | 1 | 2008 | Ramipril | Diuretics | 45% | 12 | 45 | 50 | 151 | 67 | All-cause mortality, CV |
| **Yip (HK-DHF)[24]** | 2 | 2008 | Irbesartan | | | 12 | 56 | | | 68 | mortality, HFH, 6MWD, QOL, biomarker |
| **Yusuf (CHARM-Preserved)[25]** | | 2003 | Candesartan | Placebo | 40% | 36.6 | 1514 | 1509 | 3023 | 54 | CV mortality, HFH |
| **Zi[26]** | | 2003 | Quinapril | Placebo | 40% | 6 | 36 | 38 | 74 | 59 | All-cause mortality, HFH, 6MWD |
| **Zile[27]** | | 2014 | Sitaxsentan | | 50% | 6 | 128 | 64 | 192 | 61 | HFH, exercise time, QOL |

**Supplementary Table 2**: Summary of effects for all primary and secondary outcomes by stratification

| Outcome | All-cause mortality | Cardiovascular mortality | Heart failure hospitalisation | Exercise capacity | 6MWD | $VO_2$ max | MLHFQ |
|---|---|---|---|---|---|---|---|
| **Overall** | 0.96<br>0.90 to 1.03 | 0.95<br>0.87 to 1.03 | **0.88**<br>**0.81 to 0.95** | 19.92<br>-1.30 to 41.14 | -1.94<br>-8.66 to 4.77 | -0.16<br>-0.55 to 0.24 | **-1.63**<br>**-2.94 to -0.31** |
| **Stratified by drug class** | | | | | | | |
| **Beta-blockers** | **0.78**<br>**0.65 to 0.94** | **0.75**<br>**0.60 to 0.94** | 0.67<br>0.42 to 1.07 | **39.91**<br>**14.95 to 64.87** | -26.00<br>-56.97 to 4.97 | -1.50<br>-3.36 to 0.36 | 1.00<br>-5.85 to 7.85 |
| **RAAS blockers** | 1.00<br>0.93 to 1.08 | 0.99<br>0.89 to 1.09 | **0.90**<br>**0.82 to 0.98** | -0.69<br>-23.59 to 22.20 | 1.11<br>-5.45 to 7.67 | -0.27<br>-0.95 to 0.41 | - |
| **ACE inhibitors** | 1.10<br>0.85 to 1.43 | 0.94<br>0.62 to 1.43 | 0.86<br>0.64 to 1.15 | - | - | - | -2.77<br>-7.15 to 1.61 |
| **ARB** | 1.02<br>0.93 to 1.12 | 1.02<br>0.90 to 1.14 | 0.92<br>0.83 to 1.02 | - | - | - | **-1.84**<br>**-3.55 to -0.14** |
| **MRA** | 0.92<br>0.79 to 1.08 | 0.91<br>0.74 to 1.11 | 0.84<br>0.71 to 1.00 | - | - | - | -1.39<br>-4.85 to 2.08 |
| **Others** | 0.95<br>0.78 to 1.15 | 1.02<br>0.77 to 1.35 | 0.81<br>0.64 to 1.04 | 52.96<br>-1.30 to 104.13 | -1.94<br>-8.65 to 4.77 | -0.00<br>-0.50 to 0.50 | -0.85<br>-4.49 to 2.80 |
| Stratified by follow-up duration | | | | | | | |
| **3 to 12 months** | **0.79**<br>**0.66 to 0.95** | **0.71**<br>**0.55 to 0.90** | **0.67**<br>**0.48 to 0.94** | - | - | - | -1.03<br>-2.84 to 0.78 |
| **>12 months** | 0.99<br>0.92 to 1.06 | 0.99<br>0.90 to 1.08 | **0.90**<br>**0.82 to 0.98** | - | - | - | **-2.30**<br>**-4.22 to -0.38** |
| Stratified by trial LV ejection fraction threshold | | | | | | | |
| **40 to 49%** | 0.96<br>0.88 to 1.03 | 0.95<br>0.87 to 1.03 | **0.88**<br>**0.82 to 0.96** | 17.03<br>-29.36 to 63.41 | - | **-1.29**<br>**-2.55 to -0.03** | **-1.82**<br>**-3.37 to -0.28** |
| **≥50%** | 0.99<br>0.74 to 1.32 | - | 0.51<br>0.18 to 1.48 | 11.33<br>-10.56 to 33.22 | - | -0.03<br>-0.34 to 0.28 | -1.11<br>-3.63 to 1.42 |
| Stratified by mean LV ejection fraction | | | | | | | |
| **<60%** | 0.93<br>0.82 to 1.05 | 0.90<br>0.78 to 1.05 | **0.85**<br>**0.76 to 0.94** | - | - | - | - |
| **≥60%** | 0.95<br>0.88 to 1.04 | 1.02<br>0.89 to 1.17 | 0.92<br>0.82 to 1.04 | - | - | - | - |

Data presented as risk ratios (for all-cause and cardiovascular mortality and hospitalisation outcomes) or mean difference (exercise capacity, 6MWD, VO2 max and MLHFQ), with 95% CI. 6MWD – six-minute walk distance; MLHFQ – Minnesota living with heart failure questionnaire. Only one trial with LV ejection fraction threshold ≥50% reported cardiovascular mortality.

**Supplementary Table 3**: Overview of changes to BNP and NT-pro BNP following treatment in included trials

| Author, Trial | Year | Drug | Follow-up | Study drug N | Study drug baseline | Study drug follow-up | Control N | Control baseline | Control follow-up | Mean change difference |
|---|---|---|---|---|---|---|---|---|---|---|
| **BNP** | | | | | | | | | | |
| Bergstrom, SWEDIC | 2004 | Carvedilol | 6 months | 47 | 28 | 28 | 50 | 28 | 42 | |
| Kasama | 2005 | Candesartan | 6 months | 25 | 202 | 134 | 25 | 204 | 193 | |
| Kitzman | 2010 | Enalapril | 12 months | 35 | 78 | 84 | 36 | 64 | 67 | |
| Kurrelmeyer | 2014 | Spironolactone | 6 months | 24 | 139 | 119 | 24 | 215 | 167 | |
| Mak | 2009 | Eplenerone | 12 months | 24 | 219 | 158 | 20 | 192 | 123 | |
| Parthasarathy | 2009 | Valsartan | 14 weeks | 61 | 93 | 94 | 74 | 120 | 110 | |
| Takeda | 2004 | Carvedilol | 12 months | 19 | 172 | 75 | 21 | 150 | 174 | |
| **NT-proBNP** | | | | | | | | | | |
| Cleland, PEP-CHF | 2006 | Perindopril | 2.1 years | 191 | 335 | | 184 | 453 | | -149 |
| Conraads, ELANDD | 2012 | Nebivolol | 6 months | 57 | 147 | 162 | 59 | 126 | 99 | |
| Edelman, ALDO-DHF | 2013 | Spironolactone | 12 months | 204 | 179 | 152 | 196 | 148 | 165 | |
| Massie, I-PRESERVE | 2008 | Irbesartan | 6 months | 2067 | 360 | | 2061 | 320 | | -11 |
| Redfield, RELAX | 2013 | Sildenafil | 24 weeks | 95 | 757 | | 94 | 648 | | 38 |
| Yip-1, HK-DHF | 2008 | Ramipril | 12 months | 45 | 488 | 314 | 50 | 566 | 334 | |
| Yip-2, HK-DHF | 2008 | Irbesartan | 12 months | 56 | 568 | 443 | 50 | 566 | 334 | |

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