## Model Input Parameters

### Table S1: risk equations used for clinical efficacy inputs

| Outcome | Drug | Previous events | Dist | Mean | 95% CI |
|---|---|---|---|---|---|
| CV mortality | Epl | 0 prev hosp | W | α = 0.82<br>β = 21612 | α (0.71, 0.95)<br>β = (11890, 39174) |
| | | 1 prev hosp | W | α = 0.89<br>β = 3265 | α (0.75, 1.06)<br>β = (2174,4921) |
| | | 2 prev hosp | W | α = 1.18<br>β = 2477 | α (0.90,1.54)<br>β = (1512,4058) |
| | | 3+ prev hosp | W | α = 1.91<br>β = 1244 | α (1.36,2.70)<br>β = (906,1710) |
| | Pl | 0 prev hosp | W | α = 0.82<br>β = 12200 | α (0.71, 0.95)<br>β = (7413,20023) |
| | | 1 prev hosp | W | α = 0.89<br>β = 3447 | α (0.75, 1.06)<br>β = (2318,5132) |
| | | 2 prev hosp | W | α = 1.18<br>β = 1630 | α (0.90,1.54)<br>β = (1121,2370) |
| | | 3+ prev hosp | W | α = 1.91<br>β = 1613 | α (1.36,2.70)<br>β = (1132,2301) |
| HF hospitalization | Epl | 0 prev hosp | W | α = 0.77<br>β = 9006 | α (0.71, 0.84)<br>β = (6721, 12063) |
| | | 1 prev hosp | W | α = 0.93<br>β = 190 | α (0.82, 1.05)<br>β = (142, 255) |
| | | 2 prev hosp | W | α = 1.01<br>β = 296 | α (0.79,1.30)<br>β = (183,478) |
| | | 3 prev hosp | W | α = 0.84<br>β = 136 | α (0.65,1.09)<br>β = (73,261) |
| | | 4 prev hosp | W | α = 1.06<br>β = 91 | α (0.71,1.59)<br>β = (42,197) |
| | | 5 prev hosp | W | α = 1.48<br>β = 93 | α (0.85,2.53)<br>β = (51,171) |
| | | 6 prev hosp | W | α = 1.01<br>β = 296 | α (0.79,1.30)<br>β = (183,478) |
| | | 7 prev hosp | W | α = 0.93<br>β = 190 | α (0.82, 1.05)<br>β = (142, 255) |
| | | 8+ prev hosp | W | α = 0.77<br>β = 9006 | α (0.71, 0.84)<br>β = (6721, 12063) |
| | Pl | 0 prev hosp | W | α = 0.77<br>β = 4761 | α (0.71, 0.84)<br>β = (3781,5972) |
| | | 1 prev hosp | W | α = 0.93<br>β = 174 | α (0.82, 1.05)<br>β = (139,216) |
| | | 2 prev hosp | W | α = 1.01<br>β = 336 | α (0.79,1.30)<br>β = (228,490) |
| | | 3 prev hosp | W | α = 0.84<br>β = 175 | α (0.65,1.09)<br>β = (103,299) |
| | | 4 prev hosp | W | α = 1.06<br>β =180 | α (0.71,1.59)<br>β = (95,341) |
| | | 5 prev hosp | W | α = 1.48<br>β = 98 | α (0.85,2.53)<br>β = (44,218) |
| | | 6 prev hosp | W | α = 1.01<br>β = 336 | α (0.79,1.30)<br>β = (228,490) |
| | | 7 prev hosp | W | α = 0.93<br>β = 174 | α (0.82, 1.05)<br>β = (139,216) |
| | | 8+ prev hosp | W | α = 0.77<br>β = 4761 | α (0.71, 0.84)<br>β = (3781,5972) |
| CV hospitalization | Epl | 0 prev hosp | W | α = 0.72<br>β = 8895 | α (0.66, 0.79)<br>β = (6451,12323) |

| Outcome | Drug | Previous events | Dist | Mean | 95% CI |
|---|---|---|---|---|---|
| | | 1 prev hosp | W | α = 1.00<br>β = 308 | α (0.85, 1.18)<br>β = (226,418) |
| | | 2 prev hosp | W | α = 1.01<br>β = 296 | α (0.79,1.30)<br>β = (183,478) |
| | | 3 prev hosp | W | α = 0.80<br>β = 151 | α (0.55,1.15)<br>β = (56,405) |
| | | 4 prev hosp | W | α = 1.12<br>β = 287 | α (0.55,2.24)<br>β = (98,828) |
| | | 5 prev hosp | W | α = 1.52<br>β = 110 | α (0.55,4.18)<br>β = (41,290) |
| | | 6 prev hosp | W | α = 1.00<br>β = 110 | α (1.00,1.00)<br>β = (41,290) |
| | | 7 prev hosp | W | α = 1.00<br>β = 308 | α (0.85, 1.18)<br>β = (226,418) |
| | | 8+ prev hosp | W | α = 0.72<br>β = 8895 | α (0.66, 0.79)<br>β = (6451,12323) |
| | Pl | 0 prev hosp | W | α = 0.72<br>β = 6838 | α (0.66, 0.79)<br>β = (5085,9235) |
| | | 1 prev hosp | W | α = 1.00<br>β = 343 | α (0.85, 1.18)<br>β = (255,462) |
| | | 2 prev hosp | W | α = 1.01<br>β = 336 | α (0.79,1.30)<br>β = (228,490) |
| | | 3 prev hosp | W | α = 0.80<br>β = 307 | α (0.55,1.15)<br>β = (150,627) |
| | | 4 prev hosp | W | α = 1.12<br>β = 71 | α (0.55,2.24)<br>β = (20,251) |
| | | 5 prev hosp | W | α = 1.52<br>β = 41 | α (0.55,4.18)<br>β = (11,149) |
| | | 6 prev hosp | W | α = 1.00<br>β = 41 | α (1.00,1.00)<br>β = (11,149) |
| | | 7 prev hosp | W | α = 1.00<br>β = 343 | α (0.85, 1.18)<br>β = (255,462) |
| | | 8+ prev hosp | W | α = 0.72<br>β = 6838 | α (0.66, 0.79)<br>β = (5085,9235) |
| Adverse events | Epl | 0 prev adverse event | W | α = 0.62<br>β = 11920 | α (0.56, 0.68)<br>β = (8313,17000) |
| | | 1+ prev adverse event | W | α = 0.93<br>β = 213 | α (0.77,1.13)<br>β = (154,294) |
| | P | 0 prev adverse event | W | α = 0.62<br>β = 17680 | α (0.56, 0.68)<br>β = (11693,26499) |
| | | 1+ prev adverse event | W | α = 0.93<br>β = 255 | α (0.77,1.13)<br>β = (148,339) |
| Atrial Fibrillation | Epl | n/a | E | α = 1<br>β = 25177 | β = (17823,35627) |
| | Pl | n/a | E | α = 1<br>β = 14984 | β = (11588,19526) |
| Other cause mortality | Epl & Pl | n/a | E | α = 1<br>β = 33597 | β = (26120,43262) |
| Use of devices | Epl | n/a | E | α = 1<br>β = 12326 | β = (9852,15458) |
| | Pl | n/a | E | α = 1<br>β = 10933 | β = (8733,13707) |
| Other cause discontinuation | Epl | n/a | E | α = 1<br>β = 12315 | β = (9761,15516) |

Legend: CI, confidence interval; CV cardiovascular; Dist = distribution; E = exponential; Epl = eplerenone; hosp = hospitalization; Pl = placebo; prev = previous; W = weibull.

**Covariance Information – CV Mortality, No Previous Hospitalizations**

| *Parameter* | *Coef.* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 9.409221 | 0.0641674 | -0.00926018 | 0.016412 |
| Eplerenone | 0.571797 | -0.00926018 | 0.04659389 | 0.003241 |
| ln(p) | 0.32673 | 0.01641151 | 0.00324082 | 0.005874 |

**Covariance Information – CV Mortality, One Previous Hospitalization**

| *Parameter* | *Coef.* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 8.145338 | 0.041361 | -0.02449 | 0.011904 |
| Eplerenone | -0.0543 | -0.02449 | 0.050459 | -0.00053 |
| ln(p) | 0.113993 | 0.011904 | -0.00053 | 0.008023 |

**Covariance Information – CV Mortality, Two Previous Hospitalizations**

| *Parameter* | *Coef.* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 7.396492 | 0.036133 | -0.02411 | 0.012426 |
| Eplerenone | 0.418356 | -0.02411 | 0.074785 | 0.005601 |
| ln(p) | -0.16144 | 0.012426 | 0.005601 | 0.018637 |

**Covariance Information – CV Mortality, Three Previous Hospitalizations**

| *Parameter* | *Coef.* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 7.385974 | 0.033061 | -0.02947 | 0.016034 |
| Eplerenone | -0.25983 | -0.02947 | 0.052244 | -0.00905 |
| ln(p) | 0.224237 | 0.016034 | -0.00905 | 0.03114 |

**Covariance Information – HF Hospitalization, No Previous Hospitalizations / Eight or More Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 8.468271 | 0.01372665 | -0.00446585 | 0.003679 |
| Eplerenone | 0.637353 | -0.00446585 | 0.01770232 | 0.001147 |
| ln(p) | 0.261421 | 0.00367887 | 0.00114722 | 0.001917 |

**Covariance Information – HF Hospitalization, One Previous Hospitalization / Seven or More Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 5.157638 | 0.012546 | -0.01166 | -0.00184 |
| Eplerenone | 0.090029 | -0.01166 | 0.033098 | -4.1E-05 |
| ln(p) | 0.072688 | -0.00184 | -4.1E-05 | 0.003914 |

**Covariance Information – HF Hospitalization, Two Previous Hospitalizations / Six or More Previous Hospitalisations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 5.815855 | 0.038084 | -0.036 | -0.00566 |
| Eplerenone | -0.12714 | -0.036 | 0.093316 | -0.00014 |
| ln(p) | -0.01346 | -0.00566 | -0.00014 | 0.015779 |

**Covariance Information – HF Hospitalization, Three Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 5.163061 | 0.074336 | -0.06994 | -0.01058 |
| Eplerenone | -0.23199 | -0.06994 | 0.170324 | 0.003395 |
| ln(p) | 0.177128 | -0.01058 | 0.003395 | 0.017285 |

**Covariance Information – HF Hospitalization, Four Previous Hospitalzsations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 5.194253 | 0.105528 | -0.09855 | -0.01721 |
| Eplerenone | -0.67973 | -0.09855 | 0.246259 | 0.000115 |
| ln(p) | -0.06022 | -0.01721 | 0.000115 | 0.042173 |

**Covariance Information – HF Hospitalization, Five Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 4.58036 | 0.164662 | -0.15729 | -0.02975 |
| Eplerenone | -0.04839 | -0.15728 | 0.246447 | 0.010812 |
| ln(p) | -0.38912 | -0.02975 | 0.010812 | 0.076351 |

**Covariance Information – CV Hospitalization, No Previous Hospitalizations / Eight or More Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 8.83024 | 0.02330086 | -0.009374392 | 0.005461 |
| Eplerenone | 0.262967 | -0.00937439 | 0.022752593 | 0.000564 |
| ln(p) | 0.32673 | 0.00546095 | 0.000564346 | 0.002363 |

**Covariance Information – CV Hospitalization, One Previous Hospitalization / Seven or More Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 6.282757 | 0.009851 | -0.00933 | -0.00205 |
| Eplerenone | -0.04146 | -0.00933 | 0.019187 | 0.000234 |
| ln(p) | -0.42635 | -0.00205 | 0.000234 | 0.007221 |

**Covariance Information – CV Hospitalization, Two Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 6.542929 | 0.007714 | -0.00723 | -0.0024 |
| Eplerenone | -0.16027 | -0.00723 | 0.019006 | -0.00063 |
| ln(p) | -0.80976 | -0.0024 | -0.00063 | 0.015143 |

**Covariance Information – CV Hospitalization, Three Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 6.522251 | 0.023872 | -0.02236 | -0.00762 |
| Eplerenone | -0.05888 | -0.02236 | 0.06035 | 0.00058 |
| ln(p) | -0.66069 | -0.00762 | 0.00058 | 0.035374 |

**Covariance Information – CV Hospitalization, Four Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 6.576833 | 0.136196 | -0.13092 | -0.02474 |
| Eplerenone | -0.00437 | -0.13092 | 0.220004 | -0.00546 |
| ln(p) | -0.66637 | -0.02474 | -0.00546 | 0.14173 |

**Covariance Information – CV Hospitalization, Five Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 5.92959 | 0.039843 | -0.03984 | 2.09E-18 |
| Eplerenone | 0.43647 | -0.03984 | 0.062774 | -0.02829 |
| ln(p) | -1.61141 | 2.09E-18 | -0.02829 | 0.265916 |

**Covariance Information – CV Hospitalization, Six Previous Hospitalizations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* |
|---|---|---|---|
| Constant | 5.92959 | 0.039843 | -0.03984 |
| Eplerenone | 0.43647 | -0.03984 | 0.062774 |
| ln(p) | 0 | | |

**Covariance Information – Adverse Events, No Previous Adverse Events**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 9.780193 | 0.0434739 | -0.02068822 | 0.007896 |
| Eplerenone | -0.394198 | -0.0206882 | 0.03117204 | -0.00103 |
| ln(p) | 0.482442 | 0.0078958 | -0.00103094 | 0.002379 |

**Covariance Information – Adverse Events, One Previous Adverse Event**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* | *ln(p)* |
|---|---|---|---|---|
| Constant | 5.415336 | 0.044537 | -0.04282 | -0.00436 |
| Eplerenone | -0.05508 | -0.04282 | 0.068071 | 0.000646 |
| ln(p) | 0.068987 | -0.00436 | 0.000646 | 0.009419 |

**Covariance Information – Other Cause Mortality**

| *Parameter* | *Coef* | *Constant* |
|---|---|---|
| Constant | 10.4222 | 0.0192308 |
| Eplerenone | 0 | |
| ln(p) | 0 | |

**Covariance Information – Atrial Fibrillation**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* |
|---|---|---|---|
| Constant | 9.6147 | 0.0192308 | -0.0192308 |
| Eplerenone | 0.51899 | -0.0192308 | 0.0504808 |
| ln(p) | 0 | | |

**Covariance Information – Use of Devices**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* |
|---|---|---|---|
| Constant | 9.29952 | 0.012987 | -0.012987 |
| Eplerenone | 0.11997 | -0.012987 | 0.0270715 |
| ln(p) | 0 | | |

**Covariance Information – Other Discontinuations**

| *Parameter* | *Coef* | *Constant* | *Eplerenone* |
|---|---|---|---|
| Constant | 9.516843 | 0.015873 | -0.015873 |
| Eplerenone | -0.0981954 | -0.015873 | 0.0299575 |
| ln(p) | 0 | | |

Legend: CV = cardiovascular; HF = heart failure.

## Table S2: Uncertainty for other model parameters

| Parameter | Base Case | Distribution | SE | Reference |
|---|---|---|---|---|
| *Resource Use* | | | | |
| % Receiving diuretic | 85% | Beta | 0.0068 | Patient level data from the EMPHASIS trial[1] |
| % Receiving ACE inhibitor | 78% | | 0.0080 | |
| % Receiving ARB | 19% | | 0.0075 | |
| % Receiving beta-blocker | 87% | | 0.0065 | |
| % Receiving digitalis glycosides | 27% | | 0.0085 | |
| % Receiving antiarrhythmic drug | 14% | | 0.0067 | |
| % Receiving antithrombotic drug (antiplatelet or oral anticoagulant) | 88% | | 0.0061 | |
| % Receiving lipid-lowering agent | 63% | | 0.0093 | |
| % Receiving ICD | 81% | | 0.0075 | Patient level data from the EMPHASIS trial[1] |
| % Receiving CRT | 50% | | 0.0096 | |
| Device life ICD | 5 | Uniform: 2- 9 | | Fox et al.[2] |
| Device life CRT | 6.5 | Uniform: 5-8 | | |
| % having arrhythmia | 28% | Beta | 0.0199 | Patient level data from the EMPHASIS trial[1] |
| % having myocardial infarction, unstable angina or chest pain | 32% | | 0.0208 | |
| % having stroke or TIA | 12% | | 0.0147 | |
| % having syncope/near syncope or hypotension | 8% | | 0.0117 | |
| % having cardiac tamponade, endocarditis, hypertension, valvular heart disease or other CV event | 14% | | 0.0155 | |
| % having pulmonary embolism | 1% | | 0.0034 | |
| % having other peripheral arterial problem | 5% | | 0.0096 | |
| % having ruptured aneurysm | 0% | | 0.0020 | |
| *Utilities* | | | | |
| Intercept | 0.759 | Beta | 0.040 | Gohler et al.[3] |
| Age | 0.002 | | 0.001 | |
| Male | 0.054 | | 0.009 | |
| History of diabetes | -0.041 | | 0.009 | |
| History of >2 AMIs | -0.061 | | 0.009 | |
| History of stroke/TIA | -0.074 | | 0.014 | |
| History of PVD | -0.046 | | 0.012 | |
| History of COPD | -0.035 | | 0.013 | |
| European origin | -0.060 | | 0.009 | |
| Recurrent hospitalization 1 | -0.024 | | 0.007 | |
| Recurrent hospitalization 2 | -0.031 | | 0.009 | |
| Recurrent hospitalization >=3 | -0.055 | | 0.001 | |
| Gynecomastia | -0.003 | | 0.007 | |
| Atrial fibrillation | -0.084 | + or - 30% | | Berg et al.[4] |
| *UK Costs* | | | | |
| Diuretic* | £24.78 | Uniform: £10.31 - £135.14 | | Scottish Tariff 2010-11[5] |
| ACE inhibitor* | £26.60 | Uniform: £14.94 - £40.83 | | |
| ARB* | £198.90 | Uniform: £31.05 - £480.30 | | |
| Beta-blocker* | £57.68 | Uniform £14.87 - £730.50 | | |
| Digitalis glycosides* | £14.61 | N/a – only 1 brand | | |
| Antiarrhythmic drug* | £28.96 | Uniform: £28.96 to £424.86 | | |
| Antithrombotic drug (antiplatelet or oral anticoagulant) * | £22.60 | Uniform: £10.83 to | | |

| Parameter | Base Case | Distribution | SE | Reference |
|---|---|---|---|---|
| | | £62.38 | | |
| Lipid-lowering agent* | £113.34 | Uniform: £13.18 to £343.20 | | |
| ICD | £3,666 | | £2,488 | |
| CRT | £5,738 | | £1,558 | |
| Heart failure hospitalization | £3,463 | | £1,449 | |
| Arrhythmia | £1,618 | | £1,100 | |
| Myocardial infarction, unstable Angina or chest pain | £2,545 | | £1,175 | |
| Stroke or TIA | £3,963 | | £1,529 | |
| Syncope/near syncope or hypotension | £1,255 | | £1,079 | |
| Cardiac tamponade, endocarditis, hypertension, valvular heart disease or other CV event | £4,663 | | £6,215 | |
| Pulmonary embolism | £2,682 | | £1,259 | |
| Other peripheral arterial problem | £9,201 | Gamma | £9,981 | |
| Ruptured aneurysm | £4,343 | | £1,739 | |
| Hyperkalemia - non hospitalized | £154.08 | | £0.64 | |
| Hyperkalemia - hospitalized | £652.00 | | £185.30 | |
| Hypokalemia - non hospitalized | £154.08 | | £0.64 | |
| Hypokalemia - hospitalized | £652.00 | | £185.30 | |
| Renal failure - non hospitalized | £145.39 | | £5.23 | |
| Renal failure - hospitalized | £1,011.00 | | £265.84 | |
| Hypotension - non hospitalized | £125.06 | | £57.08 | |
| Hypotension - hospitalized | £376.06 | | £69.63 | |
| Cardiology | £113.05 | | £30.50 | |
| GP visit | £53.00 | | £0.00 | |
| Biochemistry | £1.29 | | £0.41 | |
| *Spanish Costs* | | | | |
| Diuretic* | €15.71 | Uniform: €1.10 to €15.71 | | |
| ACE inhibitor* | €39.03 | Uniform: €21.18 to €82.55 | | |
| ARB* | €450.29 | Uniform: €437.57 to €456.56 | | |
| Beta-blocker* | €47.38 | Uniform: €30.68 to €78.16 | | Consejo general de colegios oficiales de farmaceuticos[6] |
| Digitalis glycosides* | €16.44 | N/a – only 1 brand | | |
| Antiarrhythmic drug* | €70.86 | | | |
| Antithrombotic drug (antiplatelet or oral anticoagulant) * | €49.31 | Uniform: €24.47 to €179.63 | | |
| Lipid-lowering agent* | €96.56 | Uniform: €40.54 to €135.51 | | |
| ICD | €8,480.76 | | €169.48 | Oblikue Consulting[7]. Callejo et al.[8] |
| CRT | €4,257.00 | | €428.59 | |
| Heart failure hospitalization | €3,320.61 | | €332.06 | |
| Arrhythmia | €1,694.76 | | €169.48 | |
| Myocardial infarction, unstable angina or chest pain | €4,285.86 | | €428.59 | |
| Stroke or TIA | €6,196.64 | Gamma | €619.66 | |
| Syncope/near syncope or hypotension | €4,482.72 | | €448.27 | Oblikue Consulting[7] |
| Cardiac tamponade, endocarditis, hypertension, valvular heart disease or other CV event | €12,976.22 | | €1,297.62 | |
| Pulmonary embolism | €4,260.80 | | €426.08 | |

| Parameter | Base Case | Distribution | SE | Reference |
|---|---|---|---|---|
| Other Peripheral Arterial Problem | €2,780.38 | | €278.04 | |
| Ruptured Aneurysm | €5,113.63 | | €511.36 | |
| Hyperkalemia - non hospitalized | €103.44 | | €10.34 | |
| Hyperkalemia - hospitalized | €103.44 | | €10.34 | |
| Hypokalemia - non hospitalized | €75.44 | | €7.54 | |
| Hypokalemia - hospitalized | €75.44 | | €7.54 | |
| Renal failure - non hospitalized | €4,505.22 | | €450.52 | |
| Renal failure - hospitalized | €4,505.22 | | €450.52 | |
| Hypotension - non hospitalized | €0.00 | | €0.00 | |
| Hypotension - hospitalized | €98.22 | | €9.82 | |
| Cardiology | €56.69 | | €5.97 | |

Legend: ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CV = cardiovascular; HF = heart failure; ICD = implantable cardioverter-defibrillator; PVD = peripheral vascular disease; SE = standard error; TIA = transient ischemic attack.
*upper and lower bounds calculated based upon the least and most expensive drug brands available

**Probabilistic Sensitivity Analysis**

A probabilistic sensitivity analysis was also carried out where input parameters for times to events, costs and utility values were assigned a probability distribution and were varied concurrently. The model was run 100 times using a Monte Carlo simulation method, randomly drawing sets of inputs from their respective distributions, producing 100 pairs of incremental effectiveness and cost results.

**Model Validation**
Three types of validation have been carried out:

- Comparison of modelled estimates of event rates within the first 21 months to EMPHASIS trial results
- Comparison of event rates from EMPHASIS with the modelled results based upon Kaplan–Meier data
- Comparison of the modelled results to available published information

**Comparison of Modelled Data to EMPHASIS Trial Results**

Table S3 shows the rates of the different events modelled over 2 years approximated to 21 months (using a ratio of 21/24) compared to the EMPHASIS trial results, which were reported for a median of 21 months. The rates of the different types of events are similar within the model and the EMPHASIS trial data for the majority of events. The modelled results, however, are consistently higher in events where recurrent incidences are modelled. This is due to the fact that censored patients do not appear to behave in the same way as uncensored patients within the trial data (i.e. patients are more likely to be censored if they have recurrent hospitalizations).

**Table S3: Comparison of modelled results with EMPHASIS results**

| | Eplerenone | | Standard care | | Difference (standard care – eplerenone) | | Difference (ratio eplerenone : standard care) | |
|---|---|---|---|---|---|---|---|---|
| | EMPHASIS* | Model* | EMPHASIS* | Model* | EMPHASIS | Model | EMPHASIS | Model |
| Cardiovascular hospitalization | 0.173 (0.142,0.205) | 0.305 (0.294,0.317) | 0.197 (0.165,0.229) | 0.338 (0.325,0.351) | 0.02 | 0.03 | 0.88 | 0.90 |
| Heart failure hospitalization | 0.200 (0.157,0.244) | 0.310 (0.297,0.323) | 0.312 (0.264,0.361) | 0.461 (0.446,0.476) | 0.11 | 0.15 | 0.64 | 0.67 |
| Cardiovascular death | 0.108 (0.089,0.127) | 0.084 (0.081,0.088) | 0.135 (0.114,0.156) | 0.119 (0.115,0.123) | 0.03 | 0.03 | 0.80 | 0.71 |
| All cause death | 0.017 (0.009,0.025) | 0.018 (0.016,0.020) | 0.020 (0.012,0.028) | 0.018 (0.017,0.020) | 0.00 | 0.00 | 0.85 | 1.00** |
| Adverse events | 0.187 (0.161,0.213) | 0.265 (0.257,0.274) | 0.142 (0.119,0.165) | 0.195 (0.187,0.202) | -0.05 | -0.07 | 1.32 | 1.36 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ICD or CRT | 0.052 (0.039,0.066) | 0.048 (0.045,0.050) | 0.056 (0.042,0.070) | 0.054 (0.051,0.057) | 0.004 | 0.006 | 0.93 | 0.89 |
| Discontinuation | 0.121 (0.102,0.141) | 0.132 (0.128,0.136) | | | | | | |

Legend: CI = confidence interval; CRT = cardiac resynchronization therapy; CV = cardiovascular; HF = heart failure; ICD = implantable cardioverter-defibrillator.
*95% CI shown in brackets; ** all cause death assumed the same for both arms in the model as no visible or significant difference in trial results

It can be seen from the above, that the model estimates a higher number of hospitalizations and adverse events relative to those reported in the EMPHASIS trial. The same applies to cardiovascular (CV) mortality. The conditional probabilities for a second or subsequent event are taken from the EMPHASIS trial so at first glance this is puzzling. We believe the explanation lies in the fact that people who have had an event, and even more so two events, are more likely to have been censored in the trial than those who have had no events. Thus the model simulates events that may well have occurred in these patients but were not recorded within EMPHASIS because the patient has been censored. Earlier parts of the simulation, before many people would have had a first event, fit the trial data well and the proportion of patients experiencing events that do not recur matches well to the trial data, therefore this is believed to be the most plausible explanation.

For all events where no interaction is assumed within the model the model predicts the EMPHASIS trial results at approximately 21 months follow-up well, with the confidence intervals for the probability of events for eplerenone and standard care overlapping and the actual events rates predicted by the model being a close estimate of the EMPHASIS trial information. Additionally when the ratios between the two treatment arms from the trial compared to the model are analyses results are consistent for the majority of endpoints with no consistent directional bias in the differences between model and trial results.

**Comparison of Modelled Data Event Rates with EMPHASIS**

Figure S1 to Figure S8 show a comparison between the modelled data for the proportion of patients experiencing an event and the data from the EMPHASIS trial. The time to first event curves fit well for the data from the beginning of the EMPHASIS trial, diverging slightly as the trial progresses. This is due to the very high level of censoring within the EMPHASIS trial at later time points (therefore data early on in the trial is given much greater weight).

**Table S4: Illustration of censoring – CV hospitalization, eplerenone**

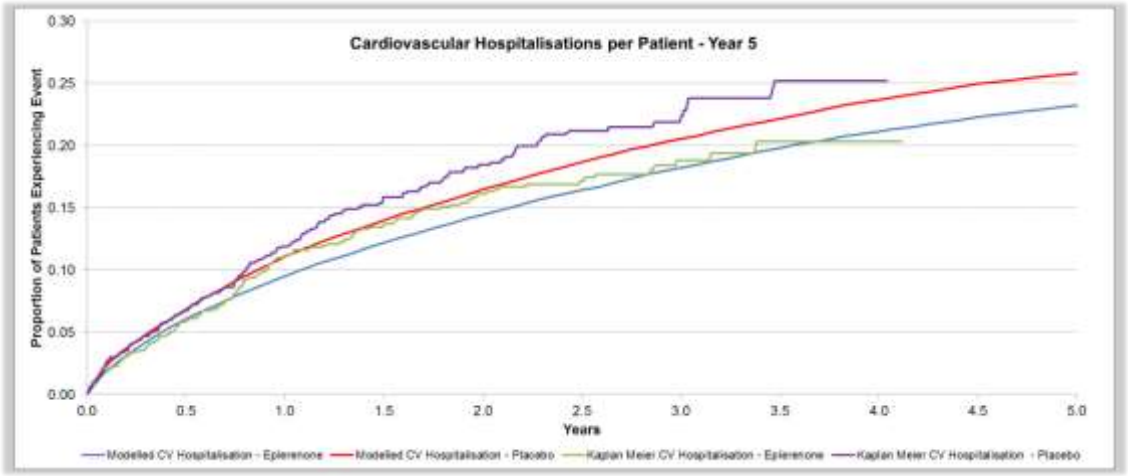
| Days | Years | Events | N in data | N no longer in data | Mean events |
|---|---|---|---|---|---|
| 50 | 0.14 | 44 | 1364 | 0 | 0.0323 |
| 150 | 0.41 | 72 | 1222 | 142 | 0.0589 |
| 250 | 0.68 | 100 | 1096 | 268 | 0.0912 |
| 350 | 0.96 | 108 | 1007 | 357 | 0.1072 |
| 450 | 1.23 | 111 | 922 | 442 | 0.1204 |
| 550 | 1.51 | 92 | 806 | 558 | 0.1141 |
| 650 | 1.78 | 91 | 721 | 643 | 0.1262 |
| 750 | 2.05 | 94 | 633 | 731 | 0.1485 |
| 850 | 2.33 | 71 | 520 | 844 | 0.1365 |
| 950 | 2.60 | 69 | 434 | 930 | 0.1590 |
| 1050 | 2.87 | 54 | 331 | 1033 | 0.1631 |
| 1150 | 3.15 | 47 | 246 | 1118 | 0.1911 |

Legend: CV = cardiovascular.

Table S4 provides an illustration of the rate of censoring within the trial. It can be seen that after 1 year the number of patients censored increases rapidly with more than half of the trial patients censored at 2 years. This illustrates why the modelled curves generally fit the beginning of the trial data well and not the end of trial information.

A high proportion of patients that have adverse events or are hospitalized due to CV or heart failure (HF) events had their treatment stopped in the clinical trial. This would not normally be a problem. However, in this study, data were collected for subsequent events within a few days of treatment being stopped but after that the data were censored. Therefore further events or death have not been recorded. Since we know from the data that a patient that has had one event is far more likely to have a subsequent event, then we are missing data on potentially a large number of events. This is the same for both arms of the trial. Therefore, the frequency of events is under reported. The clinical trial publications all concentrated on time to first event, which is unaffected by the censoring, but all events need to be considered for cost estimates. The model predictions for hospitalizations etc. should therefore be higher than those reported by the EMPHASIS trial, which they are. If data had continued to be collected for patients where treatment was stopped, it would have been easy to use these data to validate the model. Since the data were censored, there is no way of checking the model predictions precisely against actual values.

**Figure S1: Comparison of modelled and EMPHASIS trial data, CV hospitalization**




Legend: CV = cardiovascular

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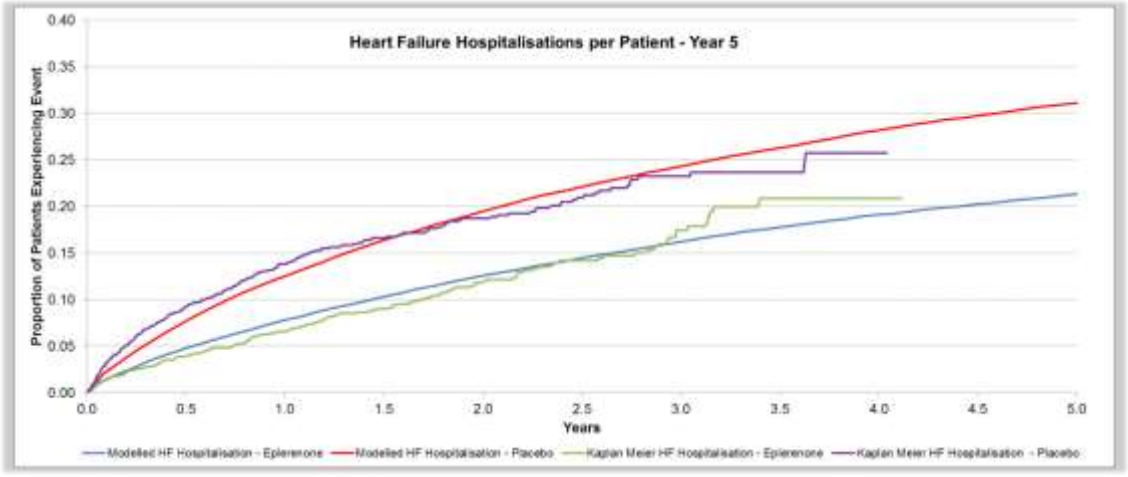
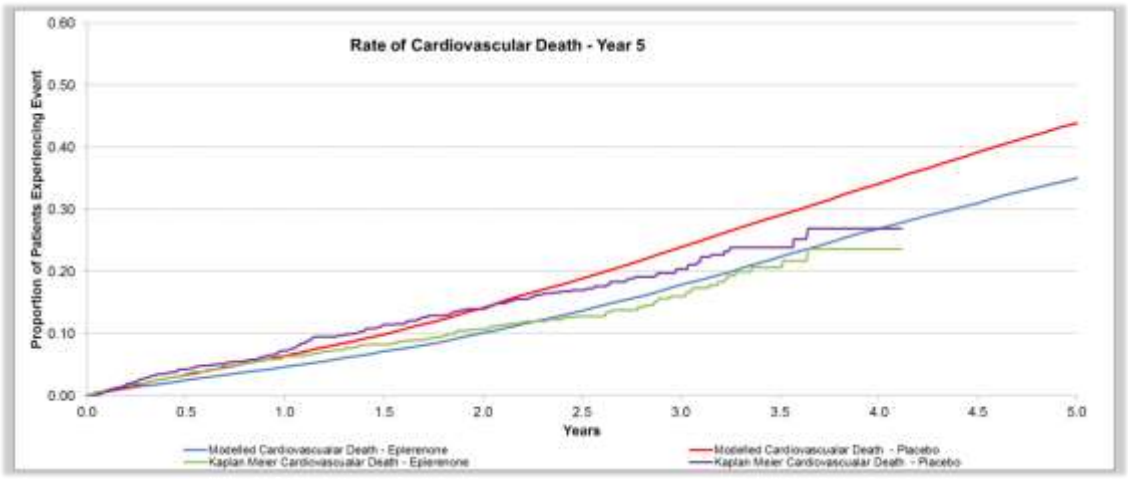
**Figure S2: Comparison of modelled and EMPHASIS trial data, HF hospitalization**




Legend: HF, heart failure.

**Figure S3: Comparison of modelled and EMPHASIS trial data, CV mortality**




Legend: CV = cardiovascular.

**Figure S4: Comparison of modelled and EMPHASIS trial data, all cause mortality**

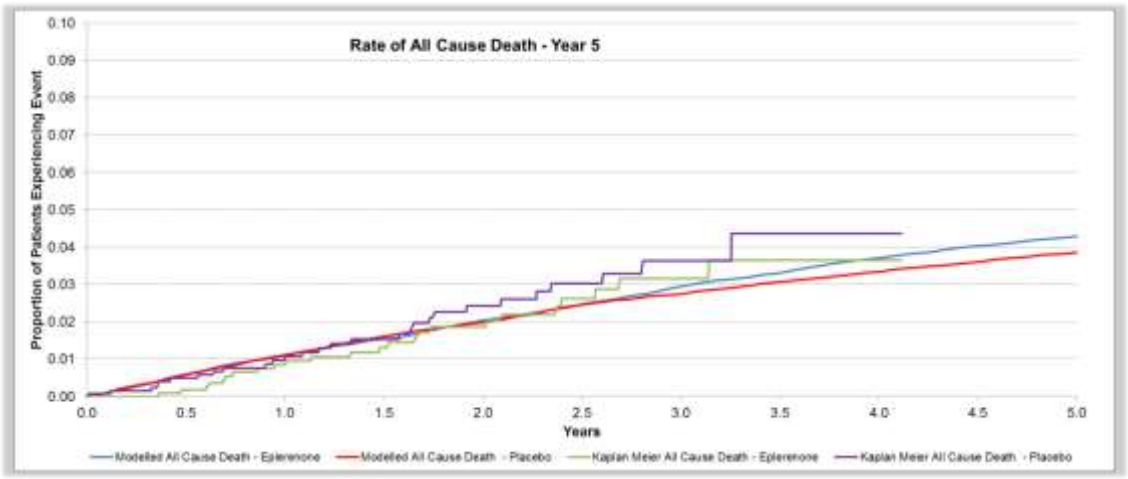



**Figure S5: Comparison of modelled and EMPHASIS trial data, adverse events**

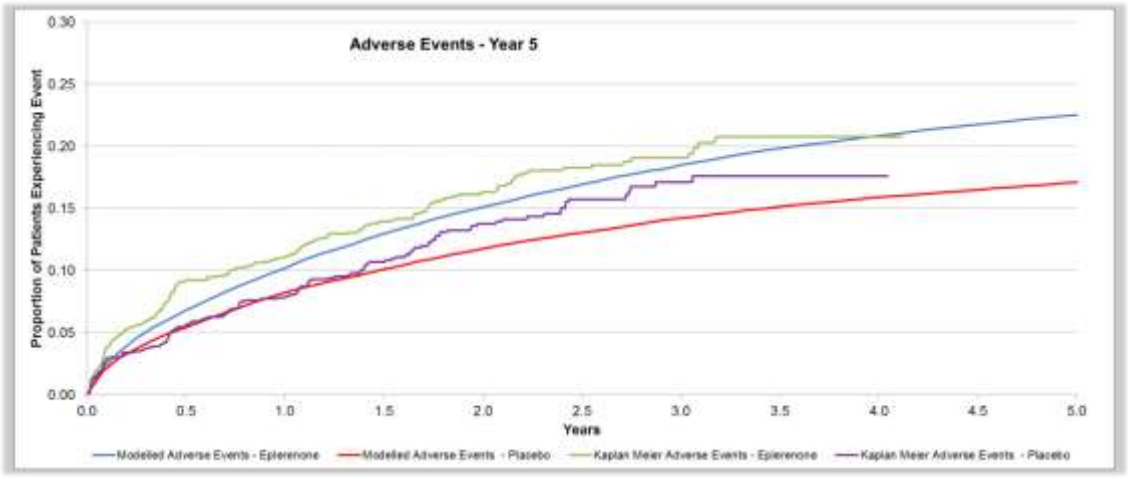
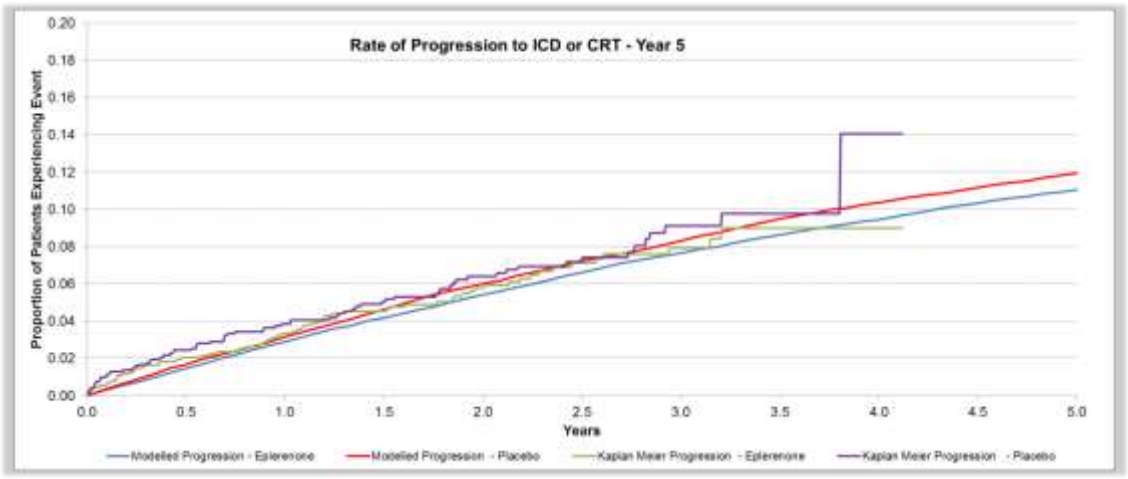


**Figure S6: Comparison of modelled and EMPHASIS trial data, use of ICD or CRT**




Legend: CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

**Figure S7: Comparison of modelled and EMPHASIS trial data, discontinuation**

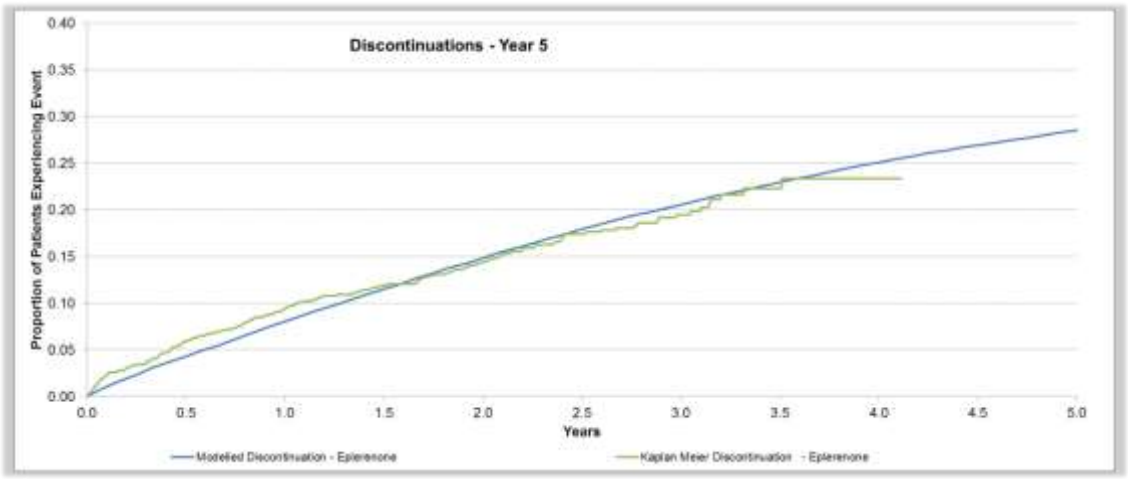
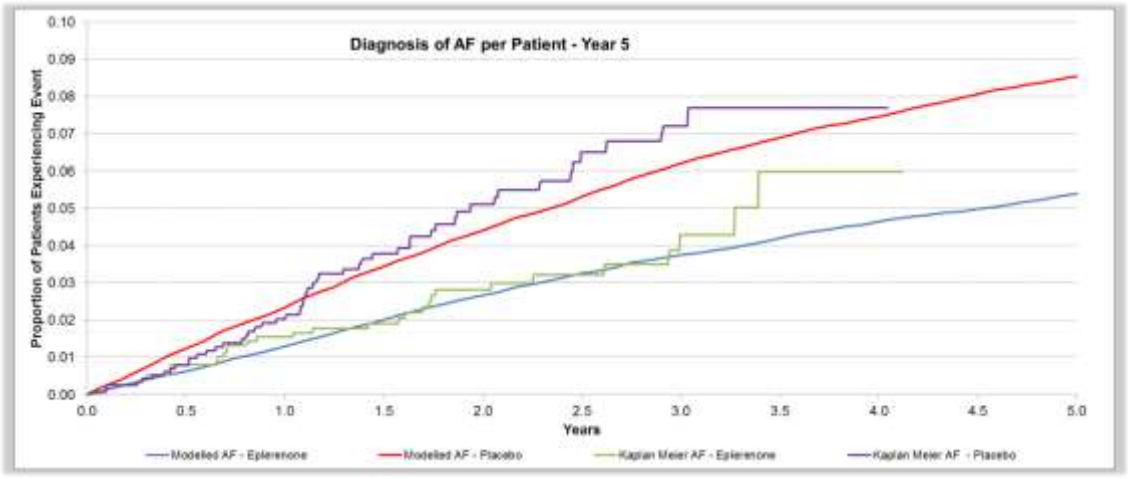



**Figure S8: Comparison of modelled and EMPHASIS trial data, diagnosis of atrial fibrillation**




Legend: AF = atrial fibrillation.

**Rationale for Cost-effectiveness Analysis**

When considering whether to fund any intervention, healthcare providers must assess if there is sufficient clinical benefit to be gained from the use of resources. Cost-effectiveness analysis is a useful tool in this process, attempting to quantify both clinical benefit and resource usage. By presenting data in terms applicable across interventions (i.e. cost per quality-adjusted life year) it allows stakeholders to make objective assessments about relative value. When combined with evaluation of numbers-needed-to-treat and budget impact analyses, cost-effectiveness data provides the payer with comprehensive evidence to inform decisions about allocation of resource. These analyses, coupled with the clinical findings from EMPHASIS-HF and other trials with mineralocorticoid receptor antagonists (MRAs) have clear implications for the management of patients with HF-REF. Not only do MRAs improve survival and reduce hospitalization, but they provide these benefits at modest additional cost to the healthcare system. There is little trade-off between the interest of the individual patient and the larger population served by the healthcare system.

**Comparison of Published Information to Trial Based Estimates for Relationship between Mortality and CV Hospitalisation**

Published information is available for a cohort of patients with HF in British Columbia by Setoguchi et al.[9] There are a few key differences between this population and the EMPHASIS trial population to which the decision problem relates:

- Older age – average age of 77 compared to EMPHASIS average age of 69
- HF population – all patients who have had a previous HF hospitalization compared to the specific EMPHASIS population of chronic systolic HF, New York Heart Association Class II and reduced left ventricular ejection fraction

In general, the data provided within the paper is supportive of the methodology used to estimate increased risk of CV mortality and shorter time to additional hospitalizations following first hospitalization within the modelling of the EMPHASIS trial data. The paper showed that, after adjusting for age, sex, and major comorbidities, the number of HF hospitalizations was a strong predictor of all-cause death.

**Table S5** Comparison of Estimated Time to Death

| | **From 1st hospitalization** | **From 2nd or more hospitalization** | **Hazard ratio from 1 hospitalization to 2 or more** |
|---|---|---|---|
| Setoguchi et al[9] | 2.4 years | 0.6 years | Between 1.22 and 1.84, adjusting for age and sex |
| EMPHASIS model* | 8 years | 4.5 years | 1.75 (between 2 & 1 hospitalizations), 1.88 (between 3 or more & 1 hospitalizations) |

* CV mortality, other cause mortality was not linked

Table S5 shows the comparison of the published information to that used within the trial. As would be expected, the trial hazard ratios are higher than the published information. This is because trial estimates are applied only to CV mortality with no impact assumed upon other mortality, whereas the estimates within the paper relate to all-cause mortality. The time to death from first hospitalization and second hospitalization within the two sources of information also make sense as the population within the published paper is 8 years older, meaning that death is likely to occur earlier.

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