**Appendix Table D159. Comparative safety of beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials**

| **Adverse Effect** | **Reference Risk of Bias** | **Active Drug**  **Dose** | **Control Drug**  **Dose** | **Events/**  **Randomized [Rate of Outcome in Active Group, %]** | **Events/**  **Randomized [Rate of Outcome in Control Group, %]** | **Relative Risk**  **(95% CI)** | **Absolute Risk Difference**  **(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Insomnia** | **Langohr, 1985184 Medium** | **Clomipramine 100mg/day** | **Metoprolol 100mg/day** | **15/63 [23.8]** | **2/63 [3.2]** | **7.5 (1.8 to 31.4)** | **0.21**  **(0.09 to 0.32)** |
| **Sweating** | **Langohr, 1985184 Medium** | **Clomipramine 100mg/day** | **Metoprolol 100mg/day** | **9/63 [14.3]** | **1/63 [1.6]** | **9.0 (1.2 to 69.0)** | **0.13**  **(0.04 to 0.22)** |
| Tiredness | Langohr, 1985184 Medium | Clomipramine 100mg/day | Metoprolol 100mg/day | 7/63 [11.1] | 9/63 [14.3] | 0.8 (0.3 to 2.0) | -0.03  (-0.15 to 0.08) |
| Constipation | Langohr, 1985184 Medium | Clomipramine 100mg/day | Metoprolol 100mg/day | 6/63 [9.5] | 1/63 [1.6] | 6.0 (0.7 to 48.4) | 0.08  (0.00 to 0.16) |
| Nausea | Langohr, 1985184 Medium | Clomipramine 100mg/day | Metoprolol 100mg/day | 5/63 [7.9] | 2/63 [3.2] | 2.5 (0.5 to 12.4) | 0.05  (-0.03 to 0.13) |
| Dizziness | Langohr, 1985184 Medium | Clomipramine 100mg/day | Metoprolol 100mg/day | 4/63 [6.3] | 1/63 [1.6] | 4.0 (0.5 to 34.8) | 0.05  (-0.02 to 0.12) |
| Loss of appetite | Langohr, 1985184 Medium | Clomipramine 100mg/day | Metoprolol 100mg/day | 3/63 [4.8] | 1/63 [1.6] | 3.0 (0.3 to 28.1) | 0.03  (-0.03 to 0.09) |
| Restlessness | Langohr, 1985184 Medium | Clomipramine 100mg/day | Metoprolol 100mg/day | 2/63 [3.2] | 2/63 [3.2] | 1.0 (0.1 to 6.9) | 0.00  (-0.06 to 0.06) |
| Adverse events | Worz, 1991186 Medium | Metoprolol 50 to 100mg twice daily | Bisoprolol 5 to 10mg once daily | 18/78 [23.1] | 23/78 [29.5] | 0.8 (0.5 to 1.3) | -0.06  (-0.20 to 0.07) |
| Dizziness | Worz, 1992187 Medium | Metoprolol 50mg BID (max. 200mg daily after 4 weeks) | Bisoprolol 5mg/day (max. 10mg daily after 4 weeks) | 4/125 [3.2] | 8/125 [6.4] | 0.5 (0.2 to 1.6) | -0.03  (-0.08 to 0.02) |
| Tiredness/fatigue | Worz, 1992187 Medium | Metoprolol 50mg BID (max. 200mg daily after 4 weeks) | Bisoprolol 5mg/day (max. 10mg daily after 4 weeks) | 7/125 [5.6] | 3/125 [2.4] | 2.3 (0.6 to 8.8) | 0.03  (-0.02 to 0.08) |
| Sleep disturbances | Worz, 1992187 Medium | Metoprolol 50mg BID (max. 200mg daily after 4 weeks) | Bisoprolol 5mg/day (max. 10mg daily after 4 weeks) | 6/125 [4.8] | 2/125 [1.6] | 3.0 (0.6 to 14.6) | 0.03  (-0.01 to 0.08) |
| Cardiovascular, hypotensive reactions | Worz, 1992187 Medium | Metoprolol 50mg BID (max. 200mg daily after 4 weeks) | Bisoprolol 5mg/day (max. 10mg daily after 4 weeks) | 1/125 [0.8] | 6/125 [4.8] | 0.2 (0.0 to 1.4) | -0.04  (-0.08 to 0.00) |
| Gastrointestinal disturbances | Worz, 1992187 Medium | Metoprolol 50mg BID (max. 200mg daily after 4 weeks) | Bisoprolol 5mg/day (max. 10mg daily after 4 weeks) | 2/125 [1.6] | 5/125 [4.0] | 0.4 (0.1 to 2.0) | -0.02  (-0.06 to 0.02) |
| Adverse effects | Worz, 1992187 Medium | Metoprolol 50mg BID (max. 200mg daily after 4 weeks) | Bisoprolol 5mg/day (max. 10mg daily after 4 weeks) | 19/125 [15.2] | 23/125 [18.4] | 0.8 (0.5 to 1.4) | -0.03  (-0.12 to 0.06) |
| Patients with treatment-related events | Schellenberg, 2008189 Medium | Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg | Nebivolol 5mg daily | 13/14 [92.9] | 11/16 [68.8] | 1.4 (0.9 to 1.9) | 0.24  (-0.02 to 0.51) |
| Patients reporting mild events | Schellenberg, 2008189 Medium | Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg | Nebivolol 5mg daily | 1/14 [7.1] | 4/16 [25.0] | 0.3 (0.0 to 2.3) | -0.18  (-0.43 to 0.07) |
| **Patients reporting moderate events** | **Schellenberg, 2008189 Medium** | **Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg** | **Nebivolol 5mg daily** | **12/14 [85.7]** | **6/16 [37.5]** | **2.3 (1.2 to 4.5)** | **0.48**  **(0.18 to 0.78)** |
| Patients reporting severe events | Schellenberg, 2008189 Medium | Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg | Nebivolol 5mg daily | 6/14 [42.9] | 2/16 [12.5] | 3.4 (0.8 to 14.3) | 0.30  (0.00 to 0.61) |
| **Fatigue** | **Schellenberg, 2008189 Medium** | **Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg** | **Nebivolol 5mg daily** | **11/14 [78.6]** | **7/16 [43.8]** | **1.8 (1.0 to 3.3)** | **0.35**  **(0.02 to 0.67)** |
| **Bradycardia** | **Schellenberg, 2008189 Medium** | **Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg** | **Nebivolol 5mg daily** | **5/14 [35.7]** | **1/16 [6.3]** | **5.7 (0.8 to 43.2)** | **0.29**  **(0.02 to 0.57)** |
| Hypotension | Schellenberg, 2008189 Medium | Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg | Nebivolol 5mg daily | 2/14 [14.3] | 1/16 [6.3] | 2.3 (0.2 to 22.6) | 0.08  (-0.14 to 0.30) |
| Supraventricular extrasystoles | Schellenberg, 2008189 Medium | Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg | Nebivolol 5mg daily | 2/14 [14.3] | 0/16 [0.0] | 5.7 (0.3 to 108.9) | 0.14  (-0.06 to 0.35) |
| At least one adverse effect | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 53/135 [39.3] | 42/135 [31.1] | 1.3 (0.9 to 1.8) | 0.08  (-0.03 to 0.19) |
| **Skin disorders** | **Diener, 2001188 Low** | **Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter)** | **Aspirin 300mg/day** | **9/135 [6.7]** | **2/135 [1.5]** | **4.5 (1.0 to 20.4)** | **0.05**  **(0.01 to 0.10)** |
| Muscular-skeletal system disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 1/135 [0.7] | 2/135 [1.5] | 0.5 (0.0 to 5.4) | -0.01  (-0.03 to 0.02) |
| Central & peripheral nervous system disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 4/135 [3.0] | 3/135 [2.2] | 1.3 (0.3 to 5.8) | 0.01  (-0.03 to 0.05) |
| **Autonomic nervous system disorders** | **Diener, 2001188 Low** | **Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter)** | **Aspirin 300mg/day** | **11/135 [8.1]** | **0/135 [0.0]** | **23.0**  **(1.4 to 386.4)** | **0.08**  **(0.03 to 0.13)** |
| Vision disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 1/135 [0.7] | 0/135 [0.0] | 3.0 (0.1 to 73.0) | 0.01  (-0.01 to 0.03) |
| Hearing and vestibular disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 1/135 [0.7] | 0/135 [0.0] | 3.0 (0.1 to 73.0) | 0.01  (-0.01 to 0.03) |
| **Psychiatric disorders** | **Diener, 2001188 Low** | **Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter)** | **Aspirin 300mg/day** | **16/135 [11.9]** | **2/135 [1.5]** | **8.0 (1.9 to 34.1)** | **0.10**  **(0.05 to 0.16)** |
| Gastrointestinal system disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 25/135 [18.5] | 30/135 [22.2] | 0.8 (0.5 to 1.3) | -0.04  (-0.13 to 0.06) |
| Liver and biliary system disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 1/135 [0.7] | 1/135 [0.7] | 1.0 (0.1 to 15.8) | 0.00  (-0.02 to 0.02) |
| Endocrine disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 0/135 [0.0] | 1/135 [0.7] | 0.3 (0.0 to 8.1) | -0.01  (-0.03 to 0.01) |
| Cardiovascular disorders, general | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 1/135 [0.7] | 0/135 [0.0] | 3.0 (0.1 to 73.0) | 0.01  (-0.01 to 0.03) |
| Vascular (extracardiac) disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 5/135 [3.7] | 0/135 [0.0] | 11.0 (0.6 to 197.0) | 0.04  (0.00 to 0.07) |
| Respiratory system disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 6/135 [4.4] | 1/135 [0.7] | 6.0 (0.7 to 49.2) | 0.04  (0.00 to 0.07) |
| White blood cell disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 2/135 [1.5] | 0/135 [0.0] | 5.0 (0.2 to 103.2) | 0.01  (-0.01 to 0.04) |
| Urinary system disorders | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 2/135 [1.5] | 4/135 [3.0] | 0.5 (0.1 to 2.7) | -0.01  (-0.05 to 0.02) |
| Reproductive disorders, female | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 2/135 [1.5] | 1/135 [0.7] | 2.0 (0.2 to 21.8) | 0.01  (-0.02 to 0.03) |
| **Body as a whole general disorders** | **Diener, 2001188 Low** | **Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter)** | **Aspirin 300mg/day** | **11/135 [8.1]** | **3/135 [2.2]** | **3.7 (1.0 to 12.9)** | **0.06**  **(0.01 to 0.11)** |
| Non-medical | Diener, 2001188 Low | Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter) | Aspirin 300mg/day | 1/135 [0.7] | 1/135 [0.7] | 1.0 (0.1 to 15.8) | 0.00  (-0.02 to 0.02) |
| **Total adverse effects** | **Diener, 2001188 Low** | **Metoprolol  200mg/day (100mg/day in the first week and 200mg/day thereafter)** | **Aspirin 300mg/day** | **99/135 [73.3]** | **51/135 [37.8]** | **1.9 (1.5 to 2.5)** | **0.36**  **(0.24 to 0.47)** |

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

CI = confidence interval