Electronic Supplementary Material

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Site-Specific Methodological Details

Inclusion and Exclusion Criteria

Treatment episodes were excluded for the following site-specific administrative reasons:

- **Danish data**: no site-specific exclusions
- **Swedish data**: reused personal identifiers
- **Clinical Practice Research Datalink (CPRD)**: treatment episodes that were identified prior to registration using an up-to-standard practice or had no follow-up time after episode initiation
- **Optum Research Database (ORD)**: treatment episodes from patients belonging to ‘administrative services only’ plans, which provides claims processing services only. Optum did not have access to identifying information for the patients in these plans, which is required to request medical records or to conduct a National Death Index (NDI) search
- **Humana**: treatment episodes from patients aged≥ 90 years, patients who belonged to a non-research eligible insurance group or patients who had conflicting sex/date of birth information on the enrolment file.

Exposure Definition

Methods for calculating total days of supply:

- In the Danish data, days of supply was estimated using waiting-time distribution [1]. This data-driven approach identified the largest interval between two prescriptions that could be assumed to belong to the same treatment episode. Any interval that exceeded this length of time was marked as a gap in treatment
- In the Swedish data, days of supply was estimated as the number of tablets in the prescription divided by the recommended daily number of tablets
In the CPRD, days of supply is rarely recorded explicitly and was therefore determined or estimated for each prescription by using a combination of available information found for that record (i.e. recorded number of days of supply, quantity of tablets prescribed, daily dose and tablet strength). When the days of supply was explicitly recorded in the data, the prescription record values were checked for plausibility against the corresponding values for the quantity of tablets prescribed and the daily administration schedule for that prescription. If the recorded days of supply value did not equal the quantity divided by the daily schedule, the calculated value was used instead.

In the ORD and Humana database, which both directly captured days of supply associated with outpatient dispensings, the total days of supply was calculated as the sum of the days of supply for all consecutive dispensings of a given medication.

**Study Outcomes**

Methods for outcome identification and ascertainment:

- In the Danish National Registers, Swedish National Registers and CPRD-linked database, the outcomes were identified through direct linkage to patient registers using International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes.
- In the CPRD-unlinked database, potential outcomes were identified based on Read codes and adjudicated by general practitioners, who provided care for patients with the potential outcomes, using questionnaires.
- In the ORD and Humana database, potential acute myocardial infarction and stroke outcomes were identified from the claims data based on the presence of International Classification of Diseases, 9th Revision or 10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) diagnosis codes in the principal (or primary) diagnosis position on at least one facility claim for hospitalisation [2, 3]. These outcomes were adjudicated through medical record review. The two different ICD versions were used due to the transition to
the 10th revision in the USA during the study period. All-cause and cardiovascular mortality were identified through linkage to the NDI [4]. The NDI contains fact, date and cause of death information. Primary and underlying causes of death are recorded using ICD-10-CM diagnosis codes.
## Reasons for Exclusion of Mirabegron and Antimuscarinic Episodes, by Individual Data Source

| Reason for episode exclusion                                  | Data source       | Episodes excluded, n (%) | Mirabegron | Antimuscarinics |
|---------------------------------------------------------------|-------------------|--------------------------|------------|-----------------|
| Prescription of the same drug in the prior 12 months          | Denmark           | 12,896 (21.1)            | 66,971 (53.9) |
|                                                               | Sweden            | 209,512 (78.0)           | 836,545 (88.9) |
|                                                               | CPRD-linked       | 6129 (33.6)              | 102,479 (56.3) |
|                                                               | CPRD-unlinked     | 9586 (33.7)              | 114,063 (53.7) |
|                                                               | Optum             | 726 (0.2)                | 1655 (< 0.1) |
|                                                               | Humana            | 30,628 (23.0)            | 845,330 (46.2) |
| < 18 years of age                                             | Denmark           | 458 (0.7)                | 3420 (2.8) |
|                                                               | Sweden            | 96 (< 0.1)               | 4764 (0.5) |
|                                                               | CPRD-linked       | 42 (0.2)                 | 3232 (1.8) |
|                                                               | CPRD-unlinked     | 4093 (1.7)               |             |
|                                                               | Optum             | 156 (< 0.1)              | 59,439 (1.6) |
|                                                               | Humana            | 5436 (4.1)               | 39,386 (2.2) |
| < 12 months of continuous enrolment in the data source        | Denmark           | 170 (0.3)                | 279 (0.2) |
|                                                               | Sweden            | 61 (< 0.1)               | 79 (< 0.1) |
|                                                               | CPRD-linked       | 713 (3.9)                | 6631 (3.6) |
|                                                               | CPRD-unlinked     | 1011 (3.6)               | 7605 (3.6) |
|                                                               | Optum             | 152,121 (39.3)           | 1,174,643 (31.3) |
|                                                               | Humana            | 58,405 (44.0)            | 611,166 (33.4) |
| Prescriptions of multiple medications on the same day         | Denmark           | 946 (1.5)                | 1221 (1.0) |
|                                                               | Sweden            | 930 (0.3)                | 1360 (0.1) |
|                                                               | CPRD-linked       | 5333 (29.2)              | 13,150 (7.2) |
|                                                               | CPRD-unlinked     | 9305 (32.7)              | 17,814 (8.4) |
|                                                               | Optum             | 306 (0.1)                | 762 (< 0.1) |
|                                                               | Humana            | 397 (0.3)                | 370 (< 0.1) |
| Non-tablet formulation                                        | Denmark           | N/A                      | 352 (0.3) |
|                                                               | Sweden            | N/A                      | 742 (0.1) |
|                                                               | CPRD-linked       | N/A                      | 5741 (3.2) |
|                                                               | CPRD-unlinked     | N/A                      | 7124 (3.4) |
|                                                               | Optum             | N/A                      | 15,715 (0.4) |
|                                                               | Humana            | N/A                      | N/A |

* n is the number of episodes excluded.
| Reason for episode exclusion                                      | Data source    | Episodes excluded,\(^a\) n (%) | Mirabegron | Antimuscarinics |
|------------------------------------------------------------------|----------------|---------------------------------|------------|-----------------|
| Site-specific reasons                                            |                |                                 |            |                 |
| PID issues                                                       | Sweden         | 275 (0.1)                       | 1666 (0.2) |                 |
| Prior registration in an up-to-standard practice                 | CPRD-linked    | 210 (1.2)                       | 3402 (1.9) |                 |
|                                                                 | CPRD-unlinked  | 181 (0.6)                       | 2685 (1.3) |                 |
| No follow-up time after episode initiation                       | CPRD-linked    | 0                               | 5 (< 0.1)  |                 |
|                                                                 | CPRD-unlinked  | 37 (< 0.1)                      |            |                 |
| Not eligible for chart requests                                  | Optum          | 204,183 (52.7)                  | 2,278,427 (60.8) |     |
| Age ≥ 90 years, non-research eligible insurance group, conflicting sex/date of birth | Humana | 8029 (6.0)                     | 116,143 (6.3) |                 |

\(^a\)Percentages were calculated using the number of OAB medication episodes identified in Fig. 1
\(^b\)The counts were combined due to small sample size within categories, in order to prevent back calculation from the number of mirabegron and antimuscarinic episodes not eligible for matching
\(^c\)Non-tablet formulations of antimuscarinics were not included in the initial step of the episode identification process and the exclusion counts are therefore not provided
\(^d\)The counts were combined due to small sample size within categories

CPRD Clinical Practice Research Datalink, N/A not applicable, OAB overactive bladder, PID personal identifiers
Adverse CV and Mortality Outcomes During Current Use of Mirabegron or Antimuscarinics (Matched Episodes), by Individual Data Source

| Outcomes                  | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | HR (95% CI)<sup>c</sup> |
|---------------------------|----------------------|-------|-------------|-------------------------------------|------------------------|
| **Danish National Registers** |                      |       |             |                                     |                        |
| MACE<sup>d</sup>          |                      |       |             |                                     |                        |
| Mirabegron                | 37,863               | 856   | 32,754      | 26.13 (24.41–27.95)                | 0.90 (0.81–0.99)       |
| Antimuscarinics           | 36,315               | 657   | 22,011      | 29.85 (27.61–32.22)                | Ref                    |
| AMI                       |                      |       |             |                                     |                        |
| Mirabegron                | 38,053               | 190   | 33,377      | 5.69 (4.91–6.56)                  | 0.90 (0.73–1.12)       |
| Antimuscarinics           | 36,547               | 144   | 22,410      | 6.43 (5.42–7.57)                  | Ref                    |
| Stroke                    |                      |       |             |                                     |                        |
| Mirabegron                | 37,923               | 573   | 32,963      | 17.38 (15.99–18.87)               | 0.92 (0.81–1.04)       |
| Antimuscarinics           | 36,405               | 429   | 22,151      | 19.37 (17.58–21.29)               | Ref                    |
| CV mortality              |                      |       |             |                                     |                        |
| Mirabegron                | 38,122               | 160   | 33,536      | 4.77 (4.06–5.57)                  | 0.79 (0.63–0.99)       |
| Antimuscarinics           | 36,647               | 140   | 22,515      | 6.22 (5.23–7.34)                  | Ref                    |
| All-cause mortality       |                      |       |             |                                     |                        |
| Mirabegron                | 38,122               | 1595  | 33,214      | 48.02 (45.69–50.44)               | 0.79 (0.73–0.84)       |
| Antimuscarinics           | 36,647               | 1362  | 22,286      | 61.12 (57.91–64.45)               | Ref                    |
| **Swedish National Registers** |                      |       |             |                                     |                        |
| MACE<sup>d</sup>          |                      |       |             |                                     |                        |
| Mirabegron                | 44,138               | 489   | 20,120      | 24.30 (22.20–26.56)               | 1.09 (0.95–1.24)       |
| Antimuscarinics           | 43,612               | 433   | 19,225      | 22.52 (20.45–24.75)               | Ref                    |
| Outcomes       | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | HR (95% CI)<sup>c</sup> |
|----------------|---------------------|-------|--------------|--------------------------------------|------------------------|
| AMI            |                     |       |              |                                      |                        |
| Mirabegron     | 44,148              | 134   | 20,229       | 6.62 (5.55–7.85)                     | 1.01 (0.79–1.28)       |
| Antimuscarinics| 43,617              | 127   | 19,328       | 6.57 (5.48–7.82)                     |                        |
| Stroke         |                     |       |              |                                      |                        |
| Mirabegron     | 44,143              | 270   | 20,160       | 13.39 (11.84–15.09)                  | 1.13 (0.95–1.35)       |
| Antimuscarinics| 43,615              | 230   | 19,277       | 11.93 (10.44–13.58)                  | Ref                    |
| CV mortality   |                     |       |              |                                      |                        |
| Mirabegron     | 44,153              | 124   | 20,269       | 6.12 (5.09–7.29)                     | 1.03 (0.80–1.33)       |
| Antimuscarinics| 43,620              | 115   | 19,380       | 5.93 (4.90–7.12)                     | Ref                    |
| All-cause mortality |                 |       |              |                                      |                        |
| Mirabegron     | 44,153              | 527   | 20,269       | 26.00 (23.83–28.32)                  | 0.79 (0.71–0.89)       |
| Antimuscarinics| 43,620              | 634   | 19,380       | 32.72 (30.22–35.36)                  | Ref                    |
| CPRD-linked    |                     |       |              |                                      |                        |
| MACE<sup>d</sup> |                 |       |              |                                      |                        |
| Mirabegron     | 5159                | 24    | 1982         | 12.11 (7.96–17.72)                   | 0.66 (0.39–1.12)       |
| Antimuscarinics| 5022                | 34    | 1831         | 18.57 (13.08–25.63)                  | Ref                    |
| AMI            |                     |       |              |                                      |                        |
| Mirabegron     | 5161                | 11    | 1984         | 5.54 (2.94–9.60)                     | 0.65 (0.30–1.40)       |
| Antimuscarinics| 5025                | 16    | 1835         | 8.72 (5.19–13.83)                    | Ref                    |
| Stroke         |                     |       |              |                                      |                        |
| Mirabegron     | 5161                | 11    | 1984         | 5.54 (2.94–9.59)                     | 0.61 (0.28–1.30)       |
| Antimuscarinics| 5023                | 17    | 1836         | 9.26 (5.60–14.49)                    | Ref                    |
| CV mortality   |                     |       |              |                                      |                        |
| Mirabegron     | 5163                | 10    | 1987         | 5.03 (2.58–8.93)                     | 0.78 (0.34–1.78)       |
| Antimuscarinics| 5026                | 12    | 1839         | 6.52 (3.56–11.05)                    | Ref                    |
| Outcomes               | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | HR (95% CI)<sup>c</sup> |
|-----------------------|----------------------|-------|--------------|-------------------------------------|--------------------------|
| **All-cause mortality** |                      |       |              |                                     |                          |
| Mirabegron            | 5163                 | 46    | 1987         | 23.15 (17.17–30.60)                 | 0.91 (0.61–1.36)         |
| Antimuscarinics       | 5026                 | 47    | 1839         | 25.55 (19.01–33.67)                 | Ref                      |
| **CPRD-unlinked**     |                      |       |              |                                     |                          |
| **MACE**              |                      |       |              |                                     |                          |
| Mirabegron            | 7577                 | 6     | 3497         | 1.72 (0.71–3.54)                    | 0.63 (0.23–1.74)         |
| Antimuscarinics       | 7335                 | 9     | 3238         | 2.78 (1.37–5.07)                    | Ref                      |
| **AMI**               |                      |       |              |                                     |                          |
| Mirabegron            | 7578                 | NR    | NR           | 0.29 (0.03–1.33)                    | 0.25 (0.03–2.17)         |
| Antimuscarinics       | 7335                 | NR    | NR           | 1.23 (0.41–2.93)                    | Ref                      |
| **Stroke**            |                      |       |              |                                     |                          |
| Mirabegron            | 7578                 | NR    | NR           | 0.86 (0.24–2.29)                    | 0.71 (0.16–3.18)         |
| Antimuscarinics       | 7335                 | NR    | NR           | 1.23 (0.41–2.93)                    | Ref                      |
| **CV mortality**      |                      |       |              |                                     |                          |
| Mirabegron            | 7579                 | NR    | NR           | 0.57 (0.11–1.83)                    | 1.75 (0.17–18.34)        |
| Antimuscarinics       | 7335                 | NR    | NR           | 0.31 (0.03–1.44)                    | Ref                      |
| **All-cause mortality** |                    |       |              |                                     |                          |
| Mirabegron            | 7579                 | 81    | 3498         | 23.15 (18.51–28.62)                 | 1.01 (0.74–1.38)         |
| Antimuscarinics       | 7335                 | 74    | 3246         | 22.80 (18.04–28.45)                 | Ref                      |
| **Optum**             |                      |       |              |                                     |                          |
| **MACE<sup>d</sup>**  |                      |       |              |                                     |                          |
| Mirabegron            | 28,295               | 183   | 9590         | 19.08 (16.47–22.00)                 | 0.92 (0.75–1.12)         |
| Antimuscarinics       | 27,609               | 211   | 10,217       | 20.65 (18.00–23.58)                 | Ref                      |
| **AMI**               |                      |       |              |                                     |                          |
| Mirabegron            | 28,308               | 28    | 9606         | 2.91 (1.98–4.15)                    | 1.04 (0.62–1.76)         |
| Outcomes              | Episodes | Cases | Person-years | Incidence rate (95% CI) | HR (95% CI) |
|-----------------------|----------|-------|--------------|-------------------------|-------------|
| **Antimuscarinics**   | 27,622   | 29    | 10,235       | 2.83 (1.94–4.01)        | Ref         |
| **Stroke**            |          |       |              |                         |             |
| Mirabegron            | 28,302   | 66    | 9597         | 6.88 (5.36–8.69)        | 0.97 (0.69–1.35) |
| Antimuscarinics       | 27,615   | 72    | 10,230       | 7.04 (5.55–8.81)        | Ref         |
| **CV mortality**      |          |       |              |                         |             |
| Mirabegron            | 28,315   | 100   | 9613         | 10.40 (8.51–12.60)      | 0.87 (0.66–1.13) |
| Antimuscarinics       | 27,629   | 123   | 10,248       | 12.00 (10.02–14.27)     | Ref         |
| **All-cause mortality**|         |       |              |                         |             |
| Mirabegron            | 28,315   | 228   | 9613         | 23.72 (20.79–26.95)     | 0.88 (0.73–1.05) |
| Antimuscarinics       | 27,629   | 277   | 10,248       | 27.03 (23.99–30.36)     | Ref         |
| **Humana**            |          |       |              |                         |             |
| MACE<sup>d</sup>      |          |       |              |                         |             |
| Mirabegron            | 28,449   | 149   | 9675         | 15.40 (13.03–18.08)     | 0.89 (0.72–1.10) |
| Antimuscarinics       | 27,966   | 192   | 11,122       | 17.26 (14.91–19.89)     | Ref         |
| **AMI**               |          |       |              |                         |             |
| Mirabegron            | 28,460   | 37    | 9690         | 3.82 (2.69–5.26)        | 0.98 (0.63–1.52) |
| Antimuscarinics       | 27,981   | 43    | 11,153       | 3.86 (2.79–5.19)        | Ref         |
| **Stroke**            |          |       |              |                         |             |
| Mirabegron            | 28,453   | 72    | 9683         | 7.44 (5.82–9.36)        | 1.27 (0.91–1.77) |
| Antimuscarinics       | 27,972   | 66    | 11,142       | 5.92 (4.58–7.54)        | Ref         |
| **CV mortality**      |          |       |              |                         |             |
| Mirabegron            | 28,466   | 50    | 9699         | 5.16 (3.83–6.80)        | 0.62 (0.44–0.86) |
| Antimuscarinics       | 27,987   | 94    | 11,173       | 8.41 (6.80–10.30)       | Ref         |
| **All-cause mortality**|         |       |              |                         |             |
| Mirabegron            | 28,466   | 259   | 9699         | 26.70 (23.55–30.16)     | 0.74 (0.63–0.86) |
| Outcomes            | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | HR (95% CI)<sup>c</sup> |
|---------------------|----------------------|-------|--------------|-------------------------------------|------------------------|
| Antimuscarinics     | 27,987               | 408   | 11,173       | 36.52 (33.06–40.24)                 | Ref                    |

AMI acute myocardial infarction, CI confidence interval, CPRD Clinical Practice Research Datalink, CV cardiovascular, HR hazard ratio, MACE major adverse cardiovascular events, NR not recorded, Ref reference group

<sup>a</sup>Where multiple individual antimuscarinic treatment episodes were joined to form a single period of current exposure, only the first matched episode during the period of current exposure was counted

<sup>b</sup>Incidence rates were calculated in terms of per 1000 person-years. CIs were calculated using Byar’s formula [5]

<sup>c</sup>HRs were calculated using Cox proportional hazard models and the corresponding Wald-based CIs were generated from the Cox models

<sup>d</sup>The number of AMI, stroke and CV mortality cases do not sum to the number of MACE cases. For patients with more than one of the individual outcomes, the earliest individual outcome was counted towards the MACE total
Adverse CV and Mortality Outcomes During Current Use of Mirabegron or Antimuscarinics (Matched Episodes),
According to Sex

| Outcomes                | Episodes   | Cases | Person-years | Incidence rate (95% CI) | Fixed effects HR (95% CI) | Random effects HR (95% CI) | I² (%) |
|-------------------------|------------|-------|--------------|-------------------------|----------------------------|----------------------------|--------|
| **Female patients**     |            |       |              |                         |                            |                            |        |
| MACEd                   |            |       |              |                         |                            |                            |        |
| Mirabegron              | 95,688     | 771   | 47,799       | 16.13 (15.02–17.30)     | 0.93 (0.84–1.03)           | 0.93 (0.84–1.03)           | 0.00    |
| Antimuscarinics         | 93,301     | 737   | 42,916       | 17.17 (15.97–18.45)     | Ref                        | Ref                        |        |
| AMI                     |            |       |              |                         |                            |                            |        |
| Mirabegron              | 95,802     | 181   | 48,126       | 3.76 (3.24–4.34)        | 1.01 (0.81–1.25)           | 1.01 (0.81–1.25)           | 0.00    |
| Antimuscarinics         | 93,428     | 155   | 43,167       | 3.59 (3.06–4.19)        | Ref                        | Ref                        |        |
| Stroke                  |            |       |              |                         |                            |                            |        |
| Mirabegron              | 95,725     | 462   | 47,914       | 9.64 (8.79–10.55)       | 1.03 (0.90–1.18)           | 1.03 (0.90–1.18)           | 0.00    |
| Antimuscarinics         | 93,343     | 387   | 43,015       | 9.00 (8.13–9.93)        | Ref                        | Ref                        |        |
| CV mortality            |            |       |              |                         |                            |                            |        |
| Mirabegron              | 95,840     | 194   | 48,227       | 4.02 (3.49–4.62)        | 0.75 (0.62–0.91)           | 0.75 (0.61–0.92)           | 11.70   |
| Antimuscarinics         | 93,473     | 249   | 43,257       | 5.76 (5.07–6.51)        | Ref                        | Ref                        |        |
| All-cause mortality     |            |       |              |                         |                            |                            |        |
| Mirabegron              | 95,840     | 1137  | 48,106       | 23.64 (22.29–25.04)     | 0.78 (0.72–0.85)           | 0.79 (0.70–0.88)           | 31.15   |
| Antimuscarinics         | 93,473     | 1241  | 43,172       | 28.75 (27.18–30.38)     | Ref                        | Ref                        |        |
| **Male patients**       |            |       |              |                         |                            |                            |        |
| MACEd                   |            |       |              |                         |                            |                            |        |
| Mirabegron              | 55,793     | 936   | 29,819       | 31.39 (29.43–33.45)     | 0.95 (0.86–1.04)           | 0.92 (0.76–1.12)           | 59.25   |
| Antimuscarinics         | 54,558     | 799   | 24,729       | 32.31 (30.13–34.61)     | Ref                        | Ref                        |        |
| Outcomes            | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | Fixed effects HR (95% CI)<sup>c</sup> | Random effects HR (95% CI)<sup>c</sup> | I² (%) |
|---------------------|-----------------------|-------|--------------|-------------------------------------|--------------------------------------|--------------------------------------|-------|
| AMI                 | Mirabegron            | 55,906| 220          | 7.27 (6.36–8.28)                    | 0.89 (0.73–1.07)                      | 0.89 (0.73–1.07)                      | 0.00  |
|                     | Antimuscarinics       | 54,699| 208          | 8.31 (7.24–9.50)                    | Ref                                  | Ref                                  |       |
| Stroke              | Mirabegron            | 55,835| 533          | 17.78 (16.32–19.34)                 | 0.97 (0.85–1.10)                      | 1.01 (0.79–1.29)                      | 45.79 |
|                     | Antimuscarinics       | 54,622| 431          | 17.34 (15.76–19.03)                 | Ref                                  | Ref                                  |       |
| CV mortality        | Mirabegron            | 55,958| 252          | 8.30 (7.32–9.37)                    | 0.91 (0.76–1.08)                      | 0.89 (0.65–1.21)                      | 53.23 |
|                     | Antimuscarinics       | 54,771| 236          | 9.39 (8.25–10.64)                   | Ref                                  | Ref                                  |       |
| All-cause mortality | Mirabegron            | 55,958| 1599         | 52.99 (50.44–55.64)                 | 0.80 (0.75–0.86)                      | 0.80 (0.75–0.86)                      | 0.00  |
|                     | Antimuscarinics       | 54,771| 1561         | 62.44 (59.40–65.60)                 | Ref                                  | Ref                                  |       |

<sup>a</sup>Where multiple individual antimuscarinic treatment episodes were joined to form a single period of current exposure, only the first matched episode during the period of current exposure was counted.

<sup>b</sup>Incidence rates were calculated in terms of per 1000 person-years. CIs were calculated using Byar’s formula [5].

<sup>c</sup>HRs and corresponding CIs were calculated using CMA Version 3 software.

<sup>d</sup>The number of AMI, stroke and CV mortality cases do not sum to the number of MACE cases. For patients with more than one of the individual outcomes, the earliest individual outcome was counted towards the MACE total.

AMI: acute myocardial infarction, CI: confidence interval, CMA: Comprehensive Meta-Analysis, CV: cardiovascular, HR: hazard ratio, MACE: major adverse cardiovascular events, Ref: reference group.
Adverse CV and Mortality Outcomes During Current Use of Mirabegron or Antimuscarinics (Matched Episodes), According to Prior History of AMI or Stroke

| Outcomes       | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | Fixed effects HR (95% CI)<sup>c</sup> | Random effects HR (95% CI)<sup>c</sup> | I<sup>2</sup> (%) |
|---------------|---------------------|-------|--------------|---------------------------------|---------------------------------|---------------------------------|----------------|
| **With a prior history of AMI or stroke** |                     |       |              |                                 |                                 |                                 |                |
| MACE<sup>d</sup> |                     |       |              |                                 |                                 |                                 |                |
| Mirabegron    | 20,352              | 692   | 10,605       | 65.25 (60.53–70.25)             | 0.93 (0.83–1.03)                | 0.93 (0.83–1.03)                | 0.00           |
| Antimuscarinics | 20,064             | 645   | 9406         | 68.57 (63.43–74.02)             | Ref                             | Ref                             |                |
| AMI           |                     |       |              |                                 |                                 |                                 |                |
| Mirabegron    | 20,570              | 135   | 11,049       | 12.22 (10.29–14.41)             | 0.86 (0.68–1.09)                | 0.86 (0.68–1.09)                | 0.00           |
| Antimuscarinics | 20,323             | 138   | 9753         | 14.15 (11.94–16.66)             | Ref                             | Ref                             |                |
| Stroke        |                     |       |              |                                 |                                 |                                 |                |
| Mirabegron    | 20,426              | 420   | 10,736       | 39.12 (35.51–43.00)             | 0.98 (0.85–1.13)                | 0.98 (0.85–1.13)                | 0.00           |
| Antimuscarinics | 20,168             | 358   | 9521         | 37.60 (33.86–41.65)             | Ref                             | Ref                             |                |
| CV mortality  |                     |       |              |                                 |                                 |                                 |                |
| Mirabegron    | 20,655              | 189   | 11,158       | 16.94 (14.65–19.49)             | 0.84 (0.69–1.03)                | 0.80 (0.57–1.14)                | 58.77          |
| Antimuscarinics | 20,438             | 210   | 9850         | 21.32 (18.58–24.35)             | Ref                             | Ref                             |                |
| All-cause mortality |           |       |              |                                 |                                 |                                 |                |
| Mirabegron    | 20,655              | 769   | 11,074       | 69.44 (64.66–74.48)             | 0.84 (0.76–0.93)                | 0.83 (0.72–0.95)                | 25.47          |
| Antimuscarinics | 20,438             | 779   | 9795         | 79.53 (74.09–85.26)             | Ref                             | Ref                             |                |
| **Without a prior history of AMI or stroke** |                     |       |              |                                 |                                 |                                 |                |
| MACE<sup>d</sup> |                     |       |              |                                 |                                 |                                 |                |
| Mirabegron    | 131,129             | 1015  | 67,013       | 15.15 (14.24–16.10)             | 0.97 (0.88–1.06)                | 0.96 (0.82–1.12)                | 53.08          |
| Antimuscarinics | 127,795            | 891   | 58,239       | 15.30 (14.32–16.33)             | Ref                             | Ref                             |                |
| Outcomes          | Episodes<sup>a</sup> | Cases | Person-years | Incidence rate (95% CI)<sup>b</sup> | Fixed effects | Random effects |  \( I^2 \) (%) |
|-------------------|----------------------|-------|--------------|--------------------------------------|---------------|---------------|----------------|
| AMI               |                      |       |              |                                      |               |               |                |
| Mirabegron        | 131,138              | 266   | 67,335       | 3.95 (3.50–4.45)                     | 1.00 (0.84–1.20) | 1.00 (0.80–1.24) | 20.61          |
| Antimuscarinics   | 127,804              | 225   | 58,450       | 3.85 (3.37–4.38)                     | Ref           | Ref           |                |
| Stroke            |                      |       |              |                                      |               |               |                |
| Mirabegron        | 131,134              | 575   | 67,150       | 8.56 (7.88–9.29)                     | 1.02 (0.90–1.16) | 1.05 (0.86–1.28) | 41.96          |
| Antimuscarinics   | 127,797              | 460   | 58,357       | 7.88 (7.19–8.63)                     | Ref           | Ref           |                |
| CV mortality      |                      |       |              |                                      |               |               |                |
| Mirabegron        | 131,143              | 257   | 67,444       | 3.81 (3.37–4.30)                     | 0.84 (0.71–1.00) | 0.84 (0.71–1.00) | 0.00           |
| Antimuscarinics   | 127,806              | 275   | 58,551       | 4.70 (4.17–5.28)                     | Ref           | Ref           |                |
| All-cause mortality |                    |       |              |                                      |               |               |                |
| Mirabegron        | 131,143              | 1967  | 67,205       | 29.27 (28.00–30.58)                  | 0.79 (0.74–0.84) | 0.79 (0.74–0.84) | 0.00           |
| Antimuscarinics   | 127,806              | 2023  | 58,376       | 34.65 (33.17–36.19)                  | Ref           | Ref           |                |

**AMI** acute myocardial infarction, **CI** confidence interval, **CMA** Comprehensive Meta-Analysis, **CV** cardiovascular, **HR** hazard ratio, **MACE** major adverse cardiovascular events, **Ref** reference group

<sup>a</sup>Where multiple individual antimuscarinic treatment episodes were joined to form a single period of current exposure, only the first matched episode during the period of current exposure was counted

<sup>b</sup>Incidence rates were calculated in terms of per 1000 person-years. CIs were calculated using Byar’s formula [5]

<sup>c</sup>HRs and corresponding CIs were calculated using CMA Version 3 software

<sup>d</sup>The number of AMI, stroke and CV mortality cases do not sum to the number of MACE cases. For patients with more than one of the individual outcomes, the earliest individual outcome was counted towards the MACE total
The Impact of Residual Confounding by Alcohol/Substance Abuse, Obesity and Tobacco Smoking, by Individual Data Source

| Data source                      | Confounding factor       | ARR | RRCD | Pc1  | Pc0  | RRadj^a | Bias (%)^b |
|----------------------------------|--------------------------|-----|------|------|------|---------|------------|
| Danish National Registers        | Alcohol/substance abuse  | 1.00| 5.5  | 0.052| 0.054| 1.006   | –0.72      |
|                                  |                          | 1.00| 5.0  | 0.052| 0.054| 1.006   | –0.66      |
|                                  |                          | 1.00| 4.5  | 0.052| 0.054| 1.005   | –0.59      |
|                                  |                          | 1.00| 4.0  | 0.052| 0.054| 1.004   | –0.52      |
|                                  |                          | 1.00| 3.5  | 0.052| 0.054| 1.003   | –0.44      |
|                                  |                          | 1.00| 3.0  | 0.052| 0.054| 1.003   | –0.36      |
|                                  |                          | 1.00| 2.5  | 0.052| 0.054| 1.002   | –0.28      |
|                                  |                          | 1.00| 2.0  | 0.052| 0.054| 1.001   | –0.19      |
|                                  |                          | 1.00| 1.5  | 0.052| 0.054| 1.000   | –0.10      |
|                                  |                          | 1.00| 1.0  | 0.052| 0.054| 0.999   | 0.00       |
| Obesity                         |                          | 1.00| 5.5  | 0.071| 0.067| 0.985   | 1.38       |
|                                  |                          | 1.00| 5.0  | 0.071| 0.067| 0.987   | 1.26       |
|                                  |                          | 1.00| 4.5  | 0.071| 0.067| 0.988   | 1.13       |
|                                  |                          | 1.00| 4.0  | 0.071| 0.067| 0.989   | 1.00       |
|                                  |                          | 1.00| 3.5  | 0.071| 0.067| 0.991   | 0.86       |
|                                  |                          | 1.00| 3.0  | 0.071| 0.067| 0.992   | 0.71       |
|                                  |                          | 1.00| 2.5  | 0.071| 0.067| 0.994   | 0.55       |
|                                  |                          | 1.00| 2.0  | 0.071| 0.067| 0.995   | 0.37       |
|                                  |                          | 1.00| 1.5  | 0.071| 0.067| 0.997   | 0.19       |
|                                  |                          | 1.00| 1.0  | 0.071| 0.067| 0.999   | 0.00       |
| Tobacco smoking                  |                          | 1.00| 5.5  | 0.070| 0.068| 0.992   | 0.69       |
|                                  |                          | 1.00| 5.0  | 0.070| 0.068| 0.993   | 0.63       |
|                                  |                          | 1.00| 4.5  | 0.070| 0.068| 0.993   | 0.57       |
|                                  |                          | 1.00| 4.0  | 0.070| 0.068| 0.994   | 0.50       |
|                                  |                          | 1.00| 3.5  | 0.070| 0.068| 0.995   | 0.43       |
|                                  |                          | 1.00| 3.0  | 0.070| 0.068| 0.995   | 0.35       |
|                                  |                          | 1.00| 2.5  | 0.070| 0.068| 0.996   | 0.27       |
|                                  |                          | 1.00| 2.0  | 0.070| 0.068| 0.997   | 0.19       |
|                                  |                          | 1.00| 1.5  | 0.070| 0.068| 0.998   | 0.10       |
|                                  |                          | 1.00| 1.0  | 0.070| 0.068| 0.999   | 0.00       |
| Data source          | Confounding factor                  | ARR  | RR<sub>CD</sub> | P<sub>C1</sub> | P<sub>C0</sub> | RR<sub>adj</sub><sup>a</sup> | Bias (%)<sup>b</sup> |
|---------------------|------------------------------------|------|-----------------|----------------|----------------|-----------------|-----------------|
| **Swedish National Registers** |                                   |      |                 |                |                |                 |                 |
| Alcohol/substance abuse | 1.05 | 5.5  | 0.007          | 0.011          | 1.065          | –1.72           |
|                      | 1.05 | 5.0  | 0.007          | 0.011          | 1.063          | –1.53           |
|                      | 1.05 | 4.5  | 0.007          | 0.011          | 1.061          | –1.35           |
|                      | 1.05 | 4.0  | 0.007          | 0.011          | 1.059          | –1.16           |
|                      | 1.05 | 3.5  | 0.007          | 0.011          | 1.057          | –0.97           |
|                      | 1.05 | 3.0  | 0.007          | 0.011          | 1.055          | –0.78           |
|                      | 1.05 | 2.5  | 0.007          | 0.011          | 1.053          | –0.59           |
|                      | 1.05 | 2.0  | 0.007          | 0.011          | 1.051          | –0.40           |
|                      | 1.05 | 1.5  | 0.007          | 0.011          | 1.049          | –0.20           |
|                      | 1.05 | 1.0  | 0.007          | 0.011          | 1.047          | 0.00            |
| Obesity              | 1.05 | 5.5  | 0.015          | 0.016          | 1.051          | –0.42           |
|                      | 1.05 | 5.0  | 0.015          | 0.016          | 1.051          | –0.38           |
|                      | 1.05 | 4.5  | 0.015          | 0.016          | 1.050          | –0.33           |
|                      | 1.05 | 4.0  | 0.015          | 0.016          | 1.050          | –0.29           |
|                      | 1.05 | 3.5  | 0.015          | 0.016          | 1.050          | –0.24           |
|                      | 1.05 | 3.0  | 0.015          | 0.016          | 1.049          | –0.19           |
|                      | 1.05 | 2.5  | 0.015          | 0.016          | 1.049          | –0.15           |
|                      | 1.05 | 2.0  | 0.015          | 0.016          | 1.048          | –0.10           |
|                      | 1.05 | 1.5  | 0.015          | 0.016          | 1.048          | –0.05           |
|                      | 1.05 | 1.0  | 0.015          | 0.016          | 1.047          | 0.00            |
| Tobacco smoking      | 1.05 | 5.5  | 0.056          | 0.060          | 1.062          | –1.42           |
|                      | 1.05 | 5.0  | 0.056          | 0.060          | 1.061          | –1.29           |
|                      | 1.05 | 4.5  | 0.056          | 0.060          | 1.059          | –1.16           |
|                      | 1.05 | 4.0  | 0.056          | 0.060          | 1.058          | –1.02           |
|                      | 1.05 | 3.5  | 0.056          | 0.060          | 1.056          | –0.87           |
|                      | 1.05 | 3.0  | 0.056          | 0.060          | 1.055          | –0.71           |
|                      | 1.05 | 2.5  | 0.056          | 0.060          | 1.053          | –0.55           |
|                      | 1.05 | 2.0  | 0.056          | 0.060          | 1.051          | –0.38           |
|                      | 1.05 | 1.5  | 0.056          | 0.060          | 1.049          | –0.19           |
|                      | 1.05 | 1.0  | 0.056          | 0.060          | 1.047          | 0.00            |
| **CPRD-linked**      |                                   |      |                 |                |                |                 |                 |
| Alcohol/substance abuse | 0.66 | 5.5  | 0.058          | 0.062          | 0.671          | –1.41           |
|                      | 0.66 | 5.0  | 0.058          | 0.062          | 0.671          | –1.28           |
|                      | 0.66 | 4.5  | 0.058          | 0.062          | 0.670          | –1.15           |
| Confounding factor | ARR | RR<sub>CD</sub> | P<sub>C1</sub> | P<sub>C0</sub> | RR<sub>adj</sub> | Bias (%) |
|--------------------|-----|----------------|-------------|-------------|----------------|----------|
| Obesity            | 0.66| 4.0           | 0.058       | 0.062       | 0.669          | –1.01    |
|                    | 0.66| 3.5           | 0.058       | 0.062       | 0.668          | –0.87    |
|                    | 0.66| 3.0           | 0.058       | 0.062       | 0.667          | –0.71    |
|                    | 0.66| 2.5           | 0.058       | 0.062       | 0.666          | –0.55    |
|                    | 0.66| 2.0           | 0.058       | 0.062       | 0.665          | –0.38    |
|                    | 0.66| 1.5           | 0.058       | 0.062       | 0.663          | –0.19    |
|                    | 0.66| 1.0           | 0.058       | 0.062       | 0.662          | 0.00     |
| Obesity            | 0.66| 5.5           | 0.196       | 0.194       | 0.659          | 0.48     |
|                    | 0.66| 5.0           | 0.196       | 0.194       | 0.659          | 0.45     |
|                    | 0.66| 4.5           | 0.196       | 0.194       | 0.659          | 0.42     |
|                    | 0.66| 4.0           | 0.196       | 0.194       | 0.659          | 0.38     |
|                    | 0.66| 3.5           | 0.196       | 0.194       | 0.660          | 0.34     |
| Obesity            | 0.66| 3.0           | 0.196       | 0.194       | 0.660          | 0.29     |
|                    | 0.66| 2.5           | 0.196       | 0.194       | 0.660          | 0.23     |
|                    | 0.66| 2.0           | 0.196       | 0.194       | 0.661          | 0.17     |
|                    | 0.66| 1.5           | 0.196       | 0.194       | 0.661          | 0.09     |
|                    | 0.66| 1.0           | 0.196       | 0.194       | 0.662          | 0.00     |
| Current smoker     | 0.66| 5.5           | 0.109       | 0.133       | 0.710          | –6.76    |
|                    | 0.66| 5.0           | 0.109       | 0.133       | 0.706          | –6.27    |
|                    | 0.66| 4.5           | 0.109       | 0.133       | 0.702          | –5.73    |
|                    | 0.66| 4.0           | 0.109       | 0.133       | 0.698          | –5.15    |
|                    | 0.66| 3.5           | 0.109       | 0.133       | 0.693          | –4.50    |
| CPRD-unlinked      | 0.66| 3.0           | 0.109       | 0.133       | 0.688          | –3.79    |
| Alcohol/substance abuse | 0.40| 5.5 | 0.041 | 0.051 | 0.413 | –3.66 |
|                     | 0.40| 5.0 | 0.041 | 0.051 | 0.412 | –3.32 |
|                     | 0.40| 4.5 | 0.041 | 0.051 | 0.410 | –2.97 |
|                     | 0.40| 4.0 | 0.041 | 0.051 | 0.409 | –2.60 |
|                     | 0.40| 3.5 | 0.041 | 0.051 | 0.407 | –2.22 |
|                     | 0.40| 3.0 | 0.041 | 0.051 | 0.405 | –1.81 |
|                     | 0.40| 2.5 | 0.041 | 0.051 | 0.404 | –1.39 |
| Data source | Confounding factor | ARR | RR<sub>CD</sub> | P<sub>C1</sub> | P<sub>C0</sub> | RR<sub>adj</sub><sup>a</sup> | Bias (%)<sup>b</sup> |
|-------------|--------------------|------|----------------|----------------|----------------|-----------------|-------------------|
| Obesity     |                    | 0.40 | 2.0           | 0.041          | 0.051          | 0.402           | −0.95            |
|             |                    | 0.40 | 1.5           | 0.041          | 0.051          | 0.400           | −0.49            |
|             | Obesity            | 0.40 | 5.5           | 0.213          | 0.206          | 0.392           | 1.63             |
|             |                    | 0.40 | 5.0           | 0.213          | 0.206          | 0.392           | 1.54             |
|             |                    | 0.40 | 4.5           | 0.213          | 0.206          | 0.392           | 1.42             |
|             |                    | 0.40 | 4.0           | 0.213          | 0.206          | 0.393           | 1.30             |
|             |                    | 0.40 | 3.5           | 0.213          | 0.206          | 0.393           | 1.16             |
|             |                    | 0.40 | 3.0           | 0.213          | 0.206          | 0.394           | 0.99             |
|             | Current smoker     | 0.40 | 5.5           | 0.130          | 0.154          | 0.425           | −6.38            |
|             |                    | 0.40 | 5.0           | 0.130          | 0.154          | 0.423           | −5.94            |
|             |                    | 0.40 | 4.5           | 0.130          | 0.154          | 0.421           | −5.46            |
|             |                    | 0.40 | 4.0           | 0.130          | 0.154          | 0.419           | −4.92            |
|             |                    | 0.40 | 3.5           | 0.130          | 0.154          | 0.416           | −4.33            |
|             |                    | 0.40 | 3.0           | 0.130          | 0.154          | 0.413           | −3.67            |
|             |                    | 0.40 | 2.5           | 0.130          | 0.154          | 0.410           | −2.92            |
|             |                    | 0.40 | 2.0           | 0.130          | 0.154          | 0.406           | −2.08            |
|             |                    | 0.40 | 1.5           | 0.130          | 0.154          | 0.402           | −1.11            |
|             |                    | 0.40 | 1.0           | 0.130          | 0.154          | 0.398           | 0.00             |
| Optum       | Alcohol/substance abuse | 0.92 | 5.5           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 5.0           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 4.5           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 4.0           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 3.5           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 3.0           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 2.5           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 2.0           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 1.5           | 0.003          | 0.003          | 0.920           | 0.00             |
|             |                    | 0.92 | 1.0           | 0.003          | 0.003          | 0.920           | 0.00             |
|             | Obesity            | 0.92 | 5.5           | 0.165          | 0.144          | 0.870           | 5.73             |
| Data source Confounding factor | ARR | RR<sub>CD</sub> | P<sub>C1</sub> | P<sub>C0</sub> | RR<sub>adj</sub><sup>a</sup> | Bias (%)<sup>b</sup> |
|-------------------------------|-----|----------------|-------------|-------------|----------------|------------------|
|                              | 0.92 | 5.0           | 0.165       | 0.144       | 0.873          | 5.33             |
| Tobacco smoking              | 0.92 | 4.5           | 0.165       | 0.144       | 0.877          | 4.89             |
|                              | 0.92 | 4.0           | 0.165       | 0.144       | 0.881          | 4.40             |
|                              | 0.92 | 3.5           | 0.165       | 0.144       | 0.886          | 3.86             |
|                              | 0.92 | 3.0           | 0.165       | 0.144       | 0.891          | 3.26             |
|                              | 0.92 | 2.5           | 0.165       | 0.144       | 0.897          | 2.59             |
|                              | 0.92 | 2.0           | 0.165       | 0.144       | 0.903          | 1.84             |
|                              | 0.92 | 1.5           | 0.165       | 0.144       | 0.911          | 0.98             |
|                              | 0.92 | 1.0           | 0.165       | 0.144       | 0.920          | 0.00             |
| Humana                       | 0.89 | 5.5           | 0.328       | 0.283       | 0.845          | 8.91             |
| Alcohol/substance abuse      | 0.89 | 5.0           | 0.328       | 0.283       | 0.848          | 8.44             |
|                              | 0.89 | 4.5           | 0.328       | 0.283       | 0.853          | 7.91             |
|                              | 0.89 | 4.0           | 0.328       | 0.283       | 0.857          | 7.30             |
|                              | 0.89 | 3.5           | 0.328       | 0.283       | 0.863          | 6.59             |
|                              | 0.89 | 3.0           | 0.328       | 0.283       | 0.870          | 5.75             |
|                              | 0.89 | 2.5           | 0.328       | 0.283       | 0.878          | 4.74             |
|                              | 0.89 | 2.0           | 0.328       | 0.283       | 0.889          | 3.51             |
|                              | 0.89 | 1.5           | 0.328       | 0.283       | 0.902          | 1.97             |
|                              | 0.89 | 1.0           | 0.328       | 0.283       | 0.920          | 0.00             |
| Obesity                      | 0.89 | 5.5           | 0.023       | 0.024       | 0.896          | −0.41            |
|                              | 0.89 | 5.0           | 0.023       | 0.024       | 0.895          | −0.36            |
|                              | 0.89 | 4.5           | 0.023       | 0.024       | 0.895          | −0.32            |
|                              | 0.89 | 4.0           | 0.023       | 0.024       | 0.895          | −0.28            |
|                              | 0.89 | 3.5           | 0.023       | 0.024       | 0.894          | −0.24            |
|                              | 0.89 | 3.0           | 0.023       | 0.024       | 0.894          | −0.19            |
|                              | 0.89 | 2.5           | 0.023       | 0.024       | 0.893          | −0.14            |
|                              | 0.89 | 2.0           | 0.023       | 0.024       | 0.893          | −0.10            |
|                              | 0.89 | 1.5           | 0.023       | 0.024       | 0.892          | −0.05            |
|                              | 0.89 | 1.0           | 0.023       | 0.024       | 0.892          | 0.00             |
|                              | 0.89 | 5.5           | 0.274       | 0.249       | 0.847          | 5.31             |
|                              | 0.89 | 5.0           | 0.274       | 0.249       | 0.849          | 5.01             |
|                              | 0.89 | 4.5           | 0.274       | 0.249       | 0.852          | 4.68             |
|                              | 0.89 | 4.0           | 0.274       | 0.249       | 0.855          | 4.29             |
|                              | 0.89 | 3.5           | 0.274       | 0.249       | 0.859          | 3.85             |
| Data source           | Arr | RR<sub>CD</sub> | P<sub>C1</sub> | P<sub>C0</sub> | RR<sub>adj</sub><sup>a</sup> | Bias (%)<sup>b</sup> |
|----------------------|-----|-----------------|----------------|----------------|----------------------|-------------------|
| Tobacco smoking      | 0.89| 3.0             | 0.274          | 0.249          | 0.863                | 3.34              |
|                      | 0.89| 2.5             | 0.274          | 0.249          | 0.868                | 2.73              |
|                      | 0.89| 2.0             | 0.274          | 0.249          | 0.874                | 2.00              |
|                      | 0.89| 1.5             | 0.274          | 0.249          | 0.882                | 1.11              |
|                      | 0.89| 1.0             | 0.274          | 0.249          | 0.892                | 0.00              |
| Tobacco smoking      | 0.89| 5.5             | 0.361          | 0.344          | 0.866                | 3.00              |
|                      | 0.89| 5.0             | 0.361          | 0.344          | 0.867                | 2.86              |
|                      | 0.89| 4.5             | 0.361          | 0.344          | 0.869                | 2.70              |
|                      | 0.89| 4.0             | 0.361          | 0.344          | 0.870                | 2.51              |
|                      | 0.89| 3.5             | 0.361          | 0.344          | 0.872                | 2.28              |
|                      | 0.89| 3.0             | 0.361          | 0.344          | 0.874                | 2.01              |
|                      | 0.89| 2.5             | 0.361          | 0.344          | 0.877                | 1.68              |
|                      | 0.89| 2.0             | 0.361          | 0.344          | 0.881                | 1.26              |
|                      | 0.89| 1.5             | 0.361          | 0.344          | 0.886                | 0.73              |
|                      | 0.89| 1.0             | 0.361          | 0.344          | 0.892                | 0.00              |

ARR apparent exposure relative risk, CPRD Clinical Practice Research Datalink, P<sub>C0</sub> prevalence of confounder among antimuscarinic episodes eligible for matching, P<sub>C1</sub> prevalence of confounder among mirabegron episodes eligible for matching, RR<sub>adj</sub> adjusted relative risk, RR<sub>CD</sub> association between confounder and disease outcome (assumed range of values)

<sup>a</sup>RR<sub>adj</sub> = ARR / ((P<sub>C1</sub> (RR<sub>CD</sub> – 1) + 1) / (P<sub>C0</sub> (RR<sub>CD</sub> – 1) + 1))

<sup>b</sup>Bias = (|ARR – RR<sub>adj</sub>| / RR<sub>adj</sub>) x 100
### Adverse CV and CV Mortality Outcomes During Current Use of Mirabegron or Antimuscarinics (Matched Episodes), Censored all Outcomes upon Occurrence of the First Individual Event

| Outcomes | Episodes | Cases | Person-years | Incidence rate (95% CI) | Fixed effects HR (95% CI) | Random effects HR (95% CI) | I² (%) |
|----------|----------|-------|--------------|-------------------------|---------------------------|----------------------------|--------|
| **MACE** |          |       |              |                         |                           |                            |        |
| Mirabegron | 151,427  | 1707  | 77,595       | 22.00 (20.97–23.06)     | 0.94 (0.88–1.01)          | 0.94 (0.84–1.04)           | 39.21  |
| Antimuscarinics | 147,820  | 1535  | 67,620       | 22.70 (21.59–23.86)     | Ref                       | Ref                        |        |
| **AMI**   |          |       |              |                         |                           |                            |        |
| Mirabegron | 151,629  | 398   | 77,379       | 5.14 (4.66–5.67)        | 0.95 (0.82–1.10)          | 0.95 (0.82–1.10)           | 0.00   |
| Antimuscarinics | 148,064  | 355   | 67,350       | 5.27 (4.74–5.84)        | Ref                       | Ref                        |        |
| **Stroke**|          |       |              |                         |                           |                            |        |
| Mirabegron | 151,494  | 988   | 77,518       | 12.75 (11.97–13.56)     | 1.01 (0.92–1.11)          | 1.02 (0.90–1.17)           | 27.60  |
| Antimuscarinics | 147,916  | 806   | 67,522       | 11.94 (11.13–12.78)     | Ref                       | Ref                        |        |
| **CV mortality** | |       |              |                         |                           |                            |        |
| Mirabegron | 151,703  | 381   | 77,282       | 4.93 (4.45–5.44)        | 0.84 (0.73–0.96)          | 0.82 (0.67–1.01)           | 39.33  |
| Antimuscarinics | 148,171  | 421   | 67,235       | 6.26 (5.69–6.88)        | Ref                       | Ref                        |        |

AMI acute myocardial infarction, CI confidence interval, CMA Comprehensive Meta-Analysis, CV cardiovascular, HR hazard ratio, MACE major adverse cardiovascular events, Ref reference group

Follow-up was censored at the first individual event. For example, if a patient had an AMI outcome, any subsequent outcomes (i.e. another AMI, stroke, CV mortality) within that episode or subsequent episodes were not counted. The AMI outcome was also counted as a MACE outcome. However, if AMI and stroke occurred at the same time, both events were counted individually, but only one event contributed to the MACE total.

Where multiple individual antimuscarinic treatment episodes were joined to form a single period of current exposure, only the first matched episode during the period of current exposure was counted.

Incidence rates were calculated in terms of per 1000 person-years. CIs were calculated using Byar’s formula [5].

HRs and corresponding CIs were calculated using CMA Version 3 software.
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