"*Supplement to: C.Foch, A. Allignol, T. Hohenberger, E. Boutmy, S. Schaefer, U. Hostalek, The effectiveness of bisoprolol versus other beta-blockers and other antihypertensive classes to treat high blood pressure: A cohort study using the UK Clinical Practice Research Datalink, Pharmacol. Res*."

# 10. Supplementary appendix A

## *10.1 Supplementary appendix: methods*

Supplementary Table . Antihypertensive drugs considered for each treatment of interest.

|  |  |
| --- | --- |
| Cohort | Antihypertensive drugs considered |
| Bisoprolol | Bisoprolol |
| Other beta-blockers | acebutolol, atenolol, betaxolol, carteolol, carvedilol, celiprolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, timolol |
| ACEi/ARB | azilsartan, candesartan, captopril, cilazapril, enalapril, eprosartan, fosinopril, imidapril, irbesartan, lisinopril, losartan, moexipril, perindopril, olmesartan, quinapril, ramipril, telmisartan, trandolapril, valsartan |
| CCB | amlodipine, diltiazem, felodipine, isradipine, lacidipine, lercanidipine, mibefradil, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil |
| Diuretics | amiloride, bendroflumethiazide, bumetanide, chlorothiazide, chlortalidone, clopamide, cyclopenthiazide, eplerenone, etacrynic acid, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide, mefruside, methyciothiazide, metolazone, piretanide,  polythiazide, spironolactone, torasemide, triamterene, xipamide |

## ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers*10.2 Supplementary appendix: results*

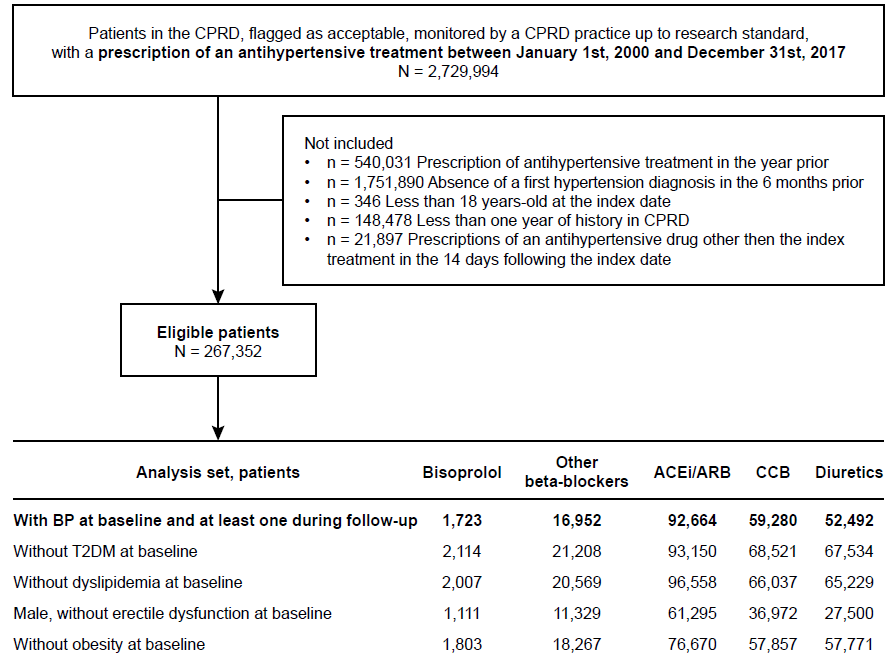
Supplementary Figure . A model showing the progress of each patient through different hypertension states over time.

BP, blood pressure

Each of the three boxes represents a state: two transient states (state 1 and 2) of controlled and uncontrolled BP; a third absorbent state (state 3) of discontinuation or death. Arrows indicate possible transitions between these states.

Supplementary Figure . Patient attrition and the number of patients in each analysis set.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; CPRD, Clinical Practice Research Datalink.



Supplementary Table 2. Baseline characteristics before matching, in patients fulfilling the study criteria.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Bisoprolol (n = 2,162)** | **Other**  **beta-blockers  (n = 21,586)** | **ACEi/ARB (n = 104,578)** | **CCB (n = 70,474)** | **Diuretics  (n = 68,552)** |
| **Demographics** |  |  |  |  |  |
| **Age, median (IQR), years** | 59 (49, 68) | 56 (48, 65) | 53 (47, 62) | 64 (57, 71) | 64 (56, 73) |
| **Male, n (%)** | 1,126 (52.1) | 11,488 (53.2) | 63,231 (60.5) | 38,064 (54.0) | 28,126 (41.0) |
| **Clinical measurement** |  |  |  |  |  |
| **BMI, median (IQR), kg/m2** | 28.2 (24.9, 32.2) | 28.4 (25.4, 31.9) | 29.6 (26.4, 33.6) | 28.2 (25.2, 31.8) | 27.9 (24.9, 31.5) |
| **Systolic BP, median (IQR), mmHg** | 160 (148, 174) | 168 (155, 180) | 160 (150, 172) | 165 (155, 180) | 168 (158, 180) |
| **Diastolic BP, median (IQR), mmHg** | 94 (85, 100) | 100 (90, 105) | 97 (90, 102) | 94 (86, 100) | 95 (88, 100) |
| **Fasting plasma glucose between ≥ 6.1 and < 7.0 mmol/L, %** | 1.0 | 0.8 | 2.1 | 1.4 | 0.8 |
| **Lifestyle risk factors** |  |  |  |  |  |
| **Current smoker, n (%)** | 342 (15.8) | 4,279 (19.8) | 20,596 (19.7) | 12,209 (17.3) | 12,484 (18.2) |

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; blood pressure, BP; CCB, calcium channel blockers; IQR, interquartile range

Supplementary Table 3. Baseline comorbidities and comedications, in patients fulfilling the study definition.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Bisoprolol (n = 2,162)** | **Other**  **beta-blockers  (n = 21,586)** | **ACEi/ARB (n = 104,578)** | **CCB (n = 70,474)** | **Diuretics  (n = 68,552)** |
| **Presence of comorbidities, n (%)** | | | | | |
| **Myocardial infarction** | 23 (1.1) | 58 (0.3) | 100 (0.1) | 14 (0.0) | 33 (0.1) |
| **Angina** | 85 (3.9) | 351 (1.6) | 172 (0.2) | 176 (0.3) | 221 (0.3) |
| **Arrhythmia** | 170 (7.9) | 198 (0.9) | 453 (0.4) | 321 (0.5) | 347 (0.5) |
| **Chronic heart failure** | 10 (0.5) | 11 (0.1) | 111 (0.1) | 23 (0.0) | 58 (0.1) |
| **Stroke** | 23 (1.7) | 135 (0.6) | 1,006 (1.0) | 547 (0.8) | 483 (0.7) |
| **Peripheral vascular disease** | 30 (1.4) | 319 (1.5) | 1,491 (1.4) | 1,492 (2.1) | 1,367 (2.0) |
| **Diabetes** | 48 (2.2) | 377 (1.8) | 11,374 (10.9) | 1,952 (2.8) | 1,016 (1.5) |
| **Dyslipidemia** | 155 (7.2) | 1,017 (4.7) | 8,020 (7.7) | 4,437 (6.3) | 3,323 (4.9) |
| **Chronic renal failure** | 29 (1.3) | 60 (0.3) | 2,149 (2.1) | 1,071 (1.5) | 400 (0.6) |
| **Depression** | 63 (2.9) | 754 (3.5) | 2,839 (2.7) | 1,289 (1.8) | 1,891 (2.8) |
| **Erectile dysfunction** | 15 (0.7) | 159 (0.7) | 1,936 (1.9) | 1,093 (1.6) | 626 (0.9) |
| **Sleep apnea** | < 5 | 18 (0.08) | 231 (0.2) | 110 (0.16) | 54 (0.1) |
| **Presence of comedications, n (%)** | | | | | |
| **Anti-coagulant** | 74 (3.4) | 151 (0.7) | 971 (0.9) | 702 (1.0) | 653 (1.0) |
| **Anti-depressant** | 311 (14.4) | 2,737 (12.7) | 14,053 (13.4) | 8,487 (12.0) | 7,963 (11.6) |
| **Anti-psychotic** | 78 (3.6) | 854 (4.0) | 3,436 (3.3) | 2,611 (3.7) | 2,977 (4.3) |
| **Platelet aggregation inhibitor** | 488 (22.6) | 2,153 (10.0) | 9,696 (9.3) | 6,505 (9.2) | 7,281 (10.6) |
| **Leading to hypertension\*** | 786 (36.4) | 8,101 (37.5) | 35,539 (34.0) | 23,317 (33.1) | 24,840 (36.2) |
| **Leading to hypotension†** | 371 (17.2) | 2,089 (9.7) | 9,155 (8.8) | 7,603 (10.8) | 5,508 (8.0) |

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers

\*Drug leading to hypertension: non-steroidal anti-inflammatory drugs, antidepressants. estrogens (hormonal birth control and hormonal replacement therapy), immunosuppressive drugs (ciclosporin, tacrolimus), methylphenidate. †Drug leading to hypotension: opioid analgesics, alpha-blockers, anti-anginals.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Bisoprolol**  **(n = 1,640)** | **Other beta-blockers  (n = 6,560)** | **Bisoprolol**  **(n = 1,929)** | **ACEi/ARB  (n = 7,716)** | **Bisoprolol**  **(n = 1,881)** | **CCB  (n = 7,524)** | **Bisoprolol**  **(n = 1,804)** | **Diuretics  (n = 7,216)** |
| **Demographics** |  |  |  |  |  |  |  |  |
| **Age, median (IQR), years** | 58 (49, 67) | 58 (49, 67) | 58 (49, 67) | 59 (49, 68) | 58 (50, 68) | 58 (49, 68) | 59 (50, 68) | 58 (49, 67.25) |
| **Male, n (%)** | 853 (52.0) | 3,468 (52.9) | 997 (51.7) | 4,051 (52.5) | 957 (50.9) | 3,973 (52.8) | 905 (50.2) | 3,548 (49.2) |
| **BMI, median (IQR), kg/m2** | 28.3 (25.4, 32.0) | 28.2 (25.1, 32.0) | 28.3 (25.0, 32.2) | 28 (24.9, 31.9) | 28.3 (25.0, 32.2) | 28.3 (25.1, 32.3) | 28.3 (25.0, 32.2) | 28.4 (25.2, 32.2) |
| **missing, %** | 59.6 | | 47.6 | | 52.3 | | 54.8 | |
| **SBP, median (IQR), mmHg** | 162  (150, 177) | 160  (150, 175) | 160  (150, 175) | 160  (150, 175) | 162  (150, 176) | 160  (150, 176) | 162  (150, 176) | 160  (150, 175) |
| **missing, %** | 5.7 | | 2.9 | | 3.3 | | 3.4 | |
| **DBP, median (IQR), mmHg** | 95 (89, 102) | 95 (86, 100) | 95 (87, 100) | 95 (86, 101) | 95 (88, 100) | 95 (87, 102) | 95 (88, 100) | 95 (88,101) |
| **missing, %** | 5.7 | | 2.9 | | 3.3 | | 3.4 | |
| **Lifestyle risk factors** |  |  |  |  |  |  |  |  |
| **Current smoker, n (%)** | 275 (16.8) | 1,103 (16.8) | 317 (16.4) | 1,406 (18.2) | 306 (16.3) | 1,298 (17.3) | 284 (15.7) | 1,218 (16.9) |
| **Presence of comorbidities, n (%)** |  |  |  |  |  |  |  |  |
| **Myocardial infarction** | 10 (0.6) | 39 (0.6) | 14 (0.7) | 59 (0.8) | < 5 | 12 (0.2) | < 5 | 23 (0.3) |
| **Angina** | 41 (2.5) | 215 (3.3) | 16 (0.8) | 105 (1.4) | 35 (1.9) | 141 (1.9) | 24 (1.3) | 123 (1.7) |
| **Arrhythmia** | 32 (2.0) | 187 (2.9) | 73 (3.8) | 382 (5.0) | 59 (3.1) | 299 (4.0) | 48 (2.7) | 275 (1.7) |
| **Chronic heart failure** | < 5 | 9 (0.1) | 7 (0.4) | 30 (0.4) | < 5 | 13 (0.2) | 5 (0.3) | 18 (0.2) |
| **Stroke** | 11 (0.7) | 67 (1.0) | 16 (0.8) | 112 (1.5) | 16 (0.9) | 97 (1.3) | 13 (0.7) | 72 (1.0) |
| **Peripheral vascular disease** | 25 (1.5) | 99 (1.5) | 27 (1.4) | 160(2.1) | 26 (1.4) | 149 (2.0) | 23 (1.3) | 131 (1.8) |
| **Dyslipidemia** | 111 (6.8) | 415 (6.3) | 128 (6.5) | 601 (7.8) | 124 (6.6) | 473 (6.3) | 113 (6.3) | 414 (5.7) |
| **Chronic renal failure** | 13 (0.8) | 51 (0.8) | 24 (1.2) | 123 (1.6) | 22 (1.2) | 108 (1.4) | 17 (0.9) | 71 (1.0) |
| **Depression** | 54 (3.3) | 213 (3.2) | 60 (3.1) | 202 (2.6) | 57 (3.0) | 219 (2.9) | 56 (3.1) | 258 (3.6) |
| **Erectile dysfunction** | 10 (0.6) | 54 (0.8) | 11 (0.6) | 71 (0.9) | 11 (0.6) | 73 (1.0) | 11 (0.6) | 78 (1.1) |
| **Sleep apnea** | < 5 | 6 (0.1) | < 5 | 15 (0.2) | < 5 | 14 (0.2) | < 5 | 7 (0.1) |
| **Presence of comedications, n (%)** |  |  |  |  |  |  |  |  |
| **Anti-coagulant** | 20 (1.2) | 89 (1.4) | 45 (2.3) | 220 (2.9) | 37 (2.0) | 155 (2.1) | 30 (1.7) | 143 (2.0) |
| **Anti-depressant** | 242 (14.8) | 899 (13.7) | 285 (14.8) | 1,088 (14.1) | 282 (15.0) | 1,119 (14.9) | 265 (14.7) | 1,044 (14.5) |
| **Anti-psychotic** | 60 (3.7) | 241 (3.7) | 71 (3.7) | 306 (4.0) | 71 (3.8) | 330 (4.4) | 67 (3.7) | 321 (4.4) |
| **Platelet aggregation inhibitor** | 276 (16.8) | 1,284 (19.6) | 356 (18.5) | 1,539 (19.9) | 344 (18.3) | 1,391 (18.5) | 306 (17.0) | 1,209 (16.8) |
| **Leading to hypertension\*** | 578 (35.2) | 2,423 (36.9) | 706 (36.6) | 2,797 (36.2) | 690 (36.7) | 2,686 (35.7) | 658 (36.5) | 2,712 (37.6) |
| **Leading to hypotension†** | 232 (14.1) | 1,035 (15.8) | 283 (14.7) | 1,163 (15.1) | 278 (14.8) | 1,065 (14.2) | 240 (13.3) | 969 (13.4) |

Supplementary Table 4. Baseline characteristics of all analysis sets, post-matching. A. Baseline characteristics and comedications after matching, in the T2DM analysis set.

A. Baseline characteristics and comedications after matching, in the T2DM analysis set.

\*Drug leading to hypertension: non-steroidal anti-inflammatory drugs, antidepressants. estrogens (hormonal birth control and hormonal replacement therapy), immunosuppressive drugs (ciclosporin, tacrolimus), methylphenidate. †Drug leading to hypotension: opioid analgesics, alpha-blockers, anti-anginals. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; T2DM, type 2 diabetes.

B. Baseline characteristics and comedications after matching, in the dyslipidemia analysis set.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Bisoprolol  (n = 1,557) | Other beta-blockers  (n = 6,308) | Bisoprolol  (n = 1,810) | ACEi/ARB (n = 7,240) | Bisoprolol  (n = 1,788) | CCB  (n = 7,152) | Bisoprolol  (n = 1,721) | Diuretics  (n = 6,884) |
| Demographics |  |  |  |  |  |  |  |  |
| Age, median (IQR), years | 58 (49, 67) | 58 (49, 67) | 58 (49, 67) | 58 (50, 68) | 58 (49, 68) | 58 (49, 68) | 58 (49, 68) | 58 (49, 67) |
| Male, n (%) | 824 (52.3) | 3,285 (52.1) | 935 (51.7) | 3,751 (51.8) | 915 (51.2) | 3,776 (52.8) | 864 (50.2) | 3,414 (49.6) |
| Clinical measurement |  |  |  |  |  |  |  |  |
| BMI, median (IQR), kg/m2 | 28.3 (25.0 32.0) | 28.2 (25.0, 32.0) | 28.3 (25.0, 32.2) | 28.0 (24.5, 32.0) | 28.3 (25.0, 32.2) | 28.4 (25.1, 32.4) | 28.3 (25.0, 32.2) | 28.3 (25.1, 31.9) |
| missing, % | 58.1 | | 58.8 | | 57.0 | | 56.4 | |
| SBP, median (IQR), mmHg | 162  (150, 178) | 160  (150, 176) | 161  (150, 176) | 160  (150, 176) | 162  (150, 176) | 161  (150, 178) | 162  (150, 178) | 162  (150, 176) |
| missing, % | 5.6 | | 5.6 | | 5.8 | | 5.4 | |
| DBP, median (IQR), mmHg | 95  (88, 102) | 95  (86, 100) | 95  (87, 100) | 95  (87, 102) | 95  (87, 100) | 95  (86, 101) | 95  (88, 100) | 95  (88, 100) |
| missing, % | 5.8 | | 5.7 | | 5.9 | | 5.5 | |
| Lifestyle risk factors |  |  |  |  |  |  |  |  |
| Current smoker, n (%) | 255 (16.2) | 1,091 (17.3) | 290 (16.0) | 1,186 (16.4) | 286 (16.0) | 1,205 (16.8) | 269 (15.6) | 1,098 (16.0) |
| Presence of comorbidities, n (%) |  |  |  |  |  |  |  |  |
| Myocardial Infarction | 10 (0.6) | 37 (0.6) | 7 (0.4) | 41 (0.6) | < 5 | 9 (0.1) | < 5 | 21 (0.3) |
| Angina | 38 (2.4) | 185 (2.9) | 13 (0.7) | 89 (1.2) | 30 (1.7) | 130 (1.8) | 21 (1.2) | 99 (1.4) |
| Arrhythmia | 35 (2.2) | 183 (2.9) | 57 (3.1) | 345 (4.8) | 54 (3.0) | 288 (4.0) | 47 (2.7) | 257 (3.7) |
| Chronic heart failure | < 5 | 10 (0.2) | 7 (0.4) | 26 (0.4) | < 5 | 15 (0.2) | < 5 | 17 (0.2) |
| Stroke | 7 (0.4) | 56 (0.9) | 11 (0.6) | 76 (1.0) | 13 (0.7) | 78(1.1) | 10 (0.6) | 66 (1.0) |
| Peripheral vascular disease | 25 (1.6) | 103 (1.6) | 25 (1.4) | 118 (1.6) | 26 (1.5) | 136 (1.9) | 22 (1.3) | 113(1.6) |
| Dyslipidemia | 27 (1.7) | 139 (2.2) | 39 (2.2) | 149 (2.1) | 33 (1.8) | 143 (2.0) | 28 (1.6) | 130 (1.9) |
| Chronic renal failure | 13 (0.8) | 41 (0.6) | 23 (1.3) | 143 (2.0) | 22 (1.2) | 108 (1.5) | 17 (1.0) | 56 (0.8) |
| Depression | 49 (3.1) | 203 (3.2) | 54 (3.0) | 196 (2.7) | 52 (2.9) | 172 (2.4) | 49 (2.8) | 253 (3.7) |
| Erectile dysfunction | 10 (0.6) | 49 (0.8) | 13 (0.7) | 62 (0.9) | 13 (0.7) | 82 (1.1) | 11 (0.6) | 74 (1.1) |
| Sleep apnea | < 5 | 6 (0.1) | < 5 | 8 (0.1) | < 5 | 13 (0.2) | < 5 | 8 (0.1) |
| Presence of comedications, n (%) |  |  |  |  |  |  |  |  |
| Anti-coagulant | 19 (1.2) | 94 (1.5) | 37 (2.0) | 183 (2.5) | 34 (1.9) | 149(2.1) | 30 (1.7) | 123 (1.8) |
| Anti-depressant | 228 (14.5) | 816 (12.9) | 265 (14.6) | 1,051 (14.5) | 268 (15.0) | 1,068 (14.9) | 250 (14.5) | 960 (13.9) |
| Anti-psychotic | 57 (3.6) | 278 (4.4) | 69 (3.8) | 243 (3.4) | 70 (3.9) | 276 (3.9) | 64 (3.7) | 307 (4.5) |
| Platelet aggregation inhibitor | 254 (16.1) | 1,158 (18.4) | 309 (17.1) | 1,318 (18.2) | 318 (17.8) | 1,315 (18.4) | 271 (15.7) | 1,144 (16.6) |
| Leading to hypertension\* | 549 (34.8) | 2,313 (36.7) | 661 (36.5) | 2,694 (37.2) | 656 (36.7) | 2,606 (36.4) | 627 (36.4) | 2,598 (37.7) |
| Leading to hypotension† | 229 (14.5) | 969 (15.4) | 261 (14.4) | 1,082 (14.9) | 266 (14.9) | 1,017 (14.2) | 222 (12.9) | 915 (13.3) |

\*Drug leading to hypertension: non-steroidal anti-inflammatory drugs, antidepressants. estrogens (hormonal birth control and hormonal replacement therapy), immunosuppressive drugs (ciclosporin, tacrolimus), methylphenidate. †Drug leading to hypotension: opioid analgesics, alpha-blockers, anti-anginals. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; T2DM, type 2 diabetes.

C. Baseline characteristics and comedications after matching, in the obesity analysis set

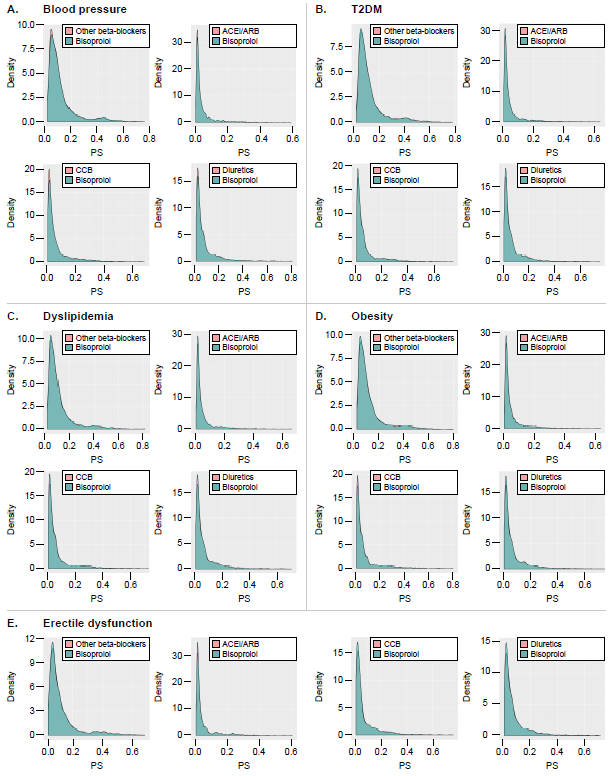
|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Bisoprolol**  **(n = 1,424)** | **Other beta-blockers  (n = 5,696)** | **Bisoprolol**  **(n = 1,612)** | **ACEi/ARB  (n = 6,448)** | **Bisoprolol**  **(n = 1,609)** | **CCB (n = 6,436)** | **Bisoprolol**  **(n = 1,524)** | **Diuretics  (n = 6,096)** |
| **Demographics** |  |  |  |  |  |  |  |  |
| **Age, median (IQR), years** | 58 (50, 68) | 59 (50, 69) | 59 (50, 68) | 59 (50, 69) | 59 (50, 69) | 59 (50, 69) | 60 (51, 69) | 59 (50, 69) |
| **Male, n (%)** | 738 (51.8) | 2,964 (52.0) | 831 (51.6) | 3307 (51.3) | 819 (50.9) | 3,328 (51.7) | 758 (49.7) | 2,981 (48.9) |
| **Clinical measurement** |  |  |  |  |  |  |  |  |
| **BMI, median (IQR), kg/m2** | 25.8 (23.6, 27.9) | 25.9 (23.5, 27.7) | 25.8 (23.5, 27.9) | 25.7 (23.2, 27.8) | 25.7 (23.4, 27.9) | 26.0 (23.6, 28.0) | 25.8 (23.5, 27.9) | 25.8 (23.4, 27.8) |
| **missing, %** | 68.2 | | 68.5 | | 62.6 | | 67.7 | |
| **SBP, median (IQR), mmHg** | 162  (150, 176) | 160  (150, 176) | 161  (150, 176) | 161  (150, 176) | 162  (150, 176) | 161  (150, 177) | 163  (150, 178) | 162  (150, 176) |
| **missing, %** | 6.2 | | 6.1 | | 3.7 | | 6.5 | |
| **DBP, median (IQR), mmHg** | 95 (88, 101) | 94 (85, 100) | 94 (86, 100) | 94 (85, 100) | 94 (86, 100) | 94 (86, 101) | 95 (88, 100) | 95 (87, 100) |
| **missing, %** | 6.4 | | 6.2 | | 3.7 | | 6.6 | |
| **Lifestyle risk factors** |  |  |  |  |  |  |  |  |
| **Current smoker, n (%)** | 237 (16.6) | 981 (17.2) | 261 (16.2) | 1,115 (17.3) | 261 (16.2) | 1,143 (17.8) | 239 (15.7) | 1,063 (17.4) |
| **Presence of comorbidities, n (%)** |  |  |  |  |  |  |  |  |
| **Myocardial infarction** | 9 (0.6) | 35 (0.6) | 11 (0.7) | 58 (0.9) | < 5 | 13 (0.2) | < 5 | 23 (0.4) |
| **Angina** | 41 (2.9) | 182 (3.2) | 12 (0.7) | 91 (1.4) | 33 (2.1) | 130 (2.0) | 22 (1.4) | 106 (1.7) |
| **Arrhythmia** | 29 (2.0) | 176 (3.1) | 50 (3.1) | 321 (5.0) | 50 (3.1) | 269 (4.2) | 43 (2.8) | 246 (4.0) |
| **Chronic heart failure** | < 5 | 8 (0.1) | 8 (0.5) | 32 (0.5) | < 5 | 12 (0.2) | < 5 | 16 (0.3) |
| **Stroke** | 9 (0.6) | 58 (1.0) | 12 (0.7) | 86 (1.3) | 14 (0.9) | 95 (1.5) | 12 (0.8) | 66 (1.1) |
| **Peripheral vascular disease** | 22 (1.5) | 107 (1.9) | 21 (1.3) | 108 (1.7) | 24 (1.5) | 146 (2.3) | 21 (1.4) | 115 (1.9) |
| **Diabetes** | 23 (1.6) | 102 (1.8) | 31 (1.9) | 107 (1.7) | 27 (1.7) | 143 (2.2) | 21 (1.4) | 91 (1.5) |
| **Dyslipidemia** | 95 (6.7) | 336 (5.9) | 102 (6.3) | 478 (7.4) | 104 (6.5) | 412 (6.4) | 96 (6.3) | 382 (6.3) |
| **Chronic renal failure** | 12 (0.8) | 45 (0.8) | 22 (1.4) | 108 (1.7) | 21 (1.3) | 96 (1.5) | 16 (1.0) | 57 (0.9) |
| **Depression** | 43 (3.0) | 191 (3.4) | 51 (3.2) | 157 (2.4) | 49 (3.0) | 169 (2.6) | 48 (3.1) | 207 (3.4) |
| **Erectile dysfunction** | 9 (0.6) | 46 (0.8) | 11 (0.7) | 85 (1.3) | 10 (0.6) | 76 (1.2) | 8 (0.5) | 62 (1.0) |
| **Sleep apnea** | < 5 | < 5 | < 5 | 8 (0.1) | < 5 | 9 (0.1) | < 5 | 5 (0.1) |
| **Presence of comedications, n (%)** |  |  |  |  |  |  |  |  |
| **Anti-coagulant** | 21 (1.5) | 84 (1.5) | 32 (2.0) | 174 (2.7) | 31 (1.9) | 126 (2.0) | 25 (1.6) | 115 (1.9) |
| **Anti-depressant** | 212 (14.9) | 808 (14.2) | 239 (14.8) | 891 (13.8) | 243 (15.1) | 930 (14.4) | 225 (14.8) | 870 (14.3) |
| **Anti-psychotic** | 53 (3.7) | 230 (4.0) | 61 (3.8) | 231 (3.6) | 64 (4.0) | 269 (4.2) | 58 (3.8) | 282 (4.6) |
| **Platelet aggregation inhibitor** | 251 (17.6) | 1,157 (20.3) | 298 (18.5) | 1,288 (20.0) | 310 (19.3) | 1,282 (19.9) | 265 (17.4) | 1,095 (18.0) |
| **Leading to hypertension\*** | 492 (34.6) | 2,108 (37.0) | 583 (36.2) | 2,345 (36.4) | 587 (36.5) | 2,261 (35.1) | 551 (36.2) | 2,331 (38.2) |
| **Leading to hypotension†** | 203 (14.3) | 878 (15.4) | 229 (14.2) | 955 (14.8) | 241 (15.0) | 881 (13.7) | 198 (13.0) | 838 (13.7) |

\*Drug leading to hypertension: non-steroidal anti-inflammatory drugs, antidepressants. estrogens (hormonal birth control and hormonal replacement therapy), immunosuppressive drugs (ciclosporin, tacrolimus), methylphenidate. †Drug leading to hypotension: opioid analgesics, alpha-blockers, anti-anginals.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Bisoprolol  (n = 879) | Other beta-blockers  (n = 3,516) | Bisoprolol  (n = 999) | ACEi/ARB  (n = 3,996) | Bisoprolol  (n = 934) | CCB  (n = 3,736) | Bisoprolol  (n = 896) | Diuretics  (n = 3,584) |
| Demographics |  |  |  |  |  |  |  |  |
| Age, median (IQR), years | 57 (48, 65) | 57 (48, 65) | 57 (48, 65) | 57 (49, 66) | 57 (49, 66) | 56 (48, 65) | 58 (49, 66) | 57 (48, 66) |
| Clinical measurement |  |  |  |  |  |  |  |  |
| BMI, median (IQR), kg/m2 | 28.6 (25.7, 31.6) | 28.6 (25.9, 31.7) | 28.7 (25.9, 32.1) | 28.8 (25.9, 32.2) | 28.7 (25.9, 31.7) | 28.8 (26.2, 32.4) | 28.6 (25.8, 31.6) | 28.7 (26.0, 31.7) |
| missing, % | 57.1 | | 58.5 | | 57.8 | | 56.5 | |
| SBP, median (IQR), mmHg | 162  (150, 174) | 160  (150, 172) | 160  (150, 171) | 160  (149, 172) | 161  (150, 172) | 160  (150, 174) | 162  (150, 174) | 160  (150, 173) |
| missing, % | 7.0 | | 6.9 | | 6.7 | | 6.6 | |
| DBP, median (IQR), mmHg | 96  (90, 102) | 96  (88, 102) | 95  (90, 102) | 95  (88, 101) | 96  (90, 102) | 96  (89, 102) | 96  (90, 102) | 96  (90, 102) |
| missing, % | 7.5 | | 7.2 | | 6.9 | | 6.7 | |
| Lifestyle risk factors |  |  |  |  |  |  |  |  |
| Current smoker, n (%) | 155 (17.6) | 673 (19.1) | 176 (17.6) | 726 (18.2) | 163 (17.5) | 732 (19.6) | 155 (17.3) | 695 (19.4) |
| Presence of comorbidities, n (%) |  |  |  |  |  |  |  |  |
| Myocardial Infarction | 8 (0.9) | 33 (0.9) | 8 (0.8) | 42 (1.1) | < 5 | 11 (0.3) | < 5 | 12 (0.3) |
| Angina | 33 (3.8) | 156 (4.4) | 9 (0.9) | 77 (1.9) | 15 (1.6) | 90 (2.4) | 10 (1.1) | 68 (1.9) |
| Arrhythmia | 21 (2.4) | 122 (3.5) | 51 (5.1) | 253 (6.3) | 28 (3.0) | 175 (4.7) | 24 (2.7) | 150 (4.2) |
| Chronic heart failure | < 5 | 7 (0.2) | 5 (0.5) | 21 (0.5) | < 5 | 9 (0.2) | < 5 | 7 (0.2) |
| Stroke | < 5 | 39 (1.1) | 6 (0.6) | 43 (1.1) | < 5 | 44 (1.2) | < 5 | 37 (1.0) |
| Peripheral vascular disease | 9 (1.0) | 62 (1.8) | 11 (1.1) | 76 (1.9) | 9 (1.0) | 72 (1.9) | 9 (1.0) | 63 (1.8) |
| Diabetes | 19 (2.2) | 74 (2.1) | 25 (2.5) | 135 (3.4) | 17 (1.8) | 114 (3.1) | 15 (1.7) | 70 (2.0) |
| Dyslipidemia | 64 (7.3) | 238 (6.8) | 71 (7.1) | 321 (8.0) | 65 (7.0) | 246 (6.6) | 61 (6.8) | 214 (6.0) |
| Chronic renal failure | 8 (0.9) | 17 (0.5) | 10 (1.0) | 60 (1.5) | 10 (1.1) | 55 (1.5) | 8 (0.9) | 24 (0.7) |
| Depression | 26 (3.0) | 88 (2.5) | 29 (2.9) | 88 (2.2) | 27 (2.9) | 86 (2.3) | 26 (2.9) | 82 (2.3) |
| Sleep apnea | < 5 | 7 (0.2) | < 5 | 10 (0.3) | < 5 | 14 (0.4) | < 5 | 5 (0.1) |
| Presence of comedications, n (%) |  |  |  |  |  |  |  |  |
| Anti-coagulant | 17 (1.9) | 60 (1.7) | 31 (3.1) | 136 (3.4) | 19 (2.0) | 76 (2.0) | 17 (1.9) | 78 (2.2) |
| Anti-depressant | 92 (10.5) | 334 (9.5) | 102 (10.2) | 425 (10.6) | 96 (10.3) | 423 (11.3) | 93 (10.4) | 366 (10.2) |
| Anti-psychotic | 24 (2.7) | 90 (2.6) | 29 (2.9) | 111 (2.8) | 27 (2.9) | 117 (3.1) | 26 (2.9) | 122 (3.4) |
| Platelet aggregation inhibitor | 181 (20.6) | 837 (23.8) | 216 (21.6) | 932 (23.3) | 185 (19.8) | 813 (21.8) | 175 (19.5) | 696 (19.4) |
| Leading to hypertension\* | 242 (27.5) | 1,043 (29.7) | 288 (28.8) | 1,202 (30.1) | 271 (29.0) | 1,142 (30.6) | 261 (29.1) | 1,063 (29.7) |
| Leading to hypotension† | 148(6.8) | 624 (7.7) | 161 (16.1) | 646 (6.2) | 152 (6.3) | 590 (5.8) | 133 (14.8) | 543 (5.2) |

D. Baseline characteristics and comedications after matching, in the erectile dysfunction analysis set.

\*Drug leading to hypertension: non-steroidal anti-inflammatory drugs, antidepressants. estrogens (hormonal birth control and hormonal replacement therapy), immunosuppressive drugs (ciclosporin, tacrolimus), methylphenidate. †Drug leading to hypotension: opioid analgesics,alpha-blockers, anti-anginals.



Supplementary Figure . Distribution of the propensity scores, after matching.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; T2DM, type 2 diabetes

A. Blood pressure; B. T2DM; C. Dyslipidemia; D. Obesity; E. Erectile dysfunction

The close overlap in propensity score distributions for each pair of cohorts in A-E suggested minimal differences between them.

Supplementary Table . Standardized mean differences before/after matching.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; SMD, standardized mean differences; T2DM, type 2 diabetes In all tables, SMD values > 0.100 (where baseline characteristics were not well-matched between comparison groups) are highlighted in bold.

1. SMD before and after matching for the variables included in the propensity score, for the BP analysis set

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Other beta-blockers versus bisoprolol** | | **ACEi/ARB versus bisoprolol** | | **CCB versus bisoprolol** | | **Diuretics versus bisoprolol** | |
| **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** |
| **Age at index** | **0.214** | 0.030 | **0.341** | 0.062 | **0.388** | 0.036 | **0.405** | 0.047 |
| **Sex = MALE** | 0.054 | 0.012 | **0.196** | 0.021 | 0.074 | 0.012 | **0.212** | 0.026 |
| **Region at index** | **0.594** | 0.090 | **0.396** | 0.085 | **0.448** | 0.056 | **0.521** | 0.085 |
| **BMI at index** | 0.031 | 0.002 | **0.279** | 0.040 | 0.004 | 0.020 | 0.054 | 0.020 |
| **Systolic blood pressure at index** | **0.302** | 0.061 | 0.003 | 0.020 | **0.257** | 0.043 | **0.296** | 0.065 |
| **Diastolic blood pressure at index** | **0.362** | 0.082 | **0.184** | 0.036 | 0.004 | 0.003 | 0.002 | 0.004 |
| **Presence of myocardial infarction at baseline** | 0.066 | 0.013 | 0.089 | 0.009 | **0.104** | 0.012 | 0.098 | 0.004 |
| **Presence of angina at baseline** | **0.135** | 0.010 | **0.261** | 0.074 | **0.255** | 0.052 | **0.242** | 0.033 |
| **Presence of arrhythmia at baseline** | **0.342** | 0.078 | **0.376** | **0.117** | **0.375** | **0.111** | **0.372** | 0.050 |
| **Presence of chronic heart failure at baseline** | 0.070 | 0.048 | 0.055 | < 0.001 | 0.074 | 0.011 | 0.067 | 0.026 |
| **Presence of stroke at baseline** | 0.042 | 0.049 | 0.004 | 0.063 | 0.024 | 0.048 | 0.027 | 0.039 |
| **Presence of peripheral vascular disease at baseline** | 0.003 | 0.015 | 0.003 | 0.033 | 0.052 | 0.031 | 0.050 | 0.044 |
| **Presence of diabetes at baseline** | 0.044 | 0.044 | **0.359** | 0.036 | 0.029 | 0.046 | 0.059 | 0.024 |
| **Presence of dyslipidemia at baseline** | **0.113** | 0.034 | 0.014 | 0.040 | 0.039 | 0.035 | 0.098 | 0.020 |
| **Presence of chronic renal failure at baseline** | **0.124** | 0.018 | 0.057 | 0.049 | 0.011 | 0.018 | 0.082 | 0.022 |
| **Presence of depression at baseline** | 0.058 | 0.010 | 0.010 | 0.045 | 0.050 | 0.007 | 0.016 | 0.032 |
| **Presence of erectile dysfunction at baseline** | 0.002 | 0.002 | 0.100 | 0.043 | 0.079 | 0.045 | 0.019 | 0.032 |
| **Presence of sleep apnea at baseline** | 0.009 | 0.006 | 0.044 | 0.016 | 0.031 | 0.033 | 0.012 | 0.037 |
| **Current smoker** | **0.102** | 0.015 | 0.084 | 0.016 | 0.026 | 0.030 | 0.049 | 0.037 |
| **Use (current or past) of anti-coagulant at baseline** | **0.188** | 0.002 | **0.163** | 0.044 | **0.157** | 0.026 | **0.159** | 0.001 |
| **Use of anti-depressant at baseline** | 0.053 | 0.037 | 0.032 | 0.038 | 0.075 | 0.006 | 0.086 | 0.033 |
| **Use of anti-psychotic at baseline** | 0.007 | 0.003 | 0.027 | 0.014 | 0.005 | 0.025 | 0.032 | 0.016 |
| **Use of medication(s) leading to hypertension at baseline** | 0.012 | 0.060 | 0.065 | 0.022 | 0.083 | 0.012 | 0.012 | 0.035 |
| **Use of medication(s) leading to hypotension at baseline** | **0.214** | 0.016 | **0.240** | 0.030 | **0.175** | 0.004 | **0.266** | 0.020 |
| **Use of platelet aggregation inhibitor at baseline** | **0.330** | 0.050 | **0.347** | 0.033 | **0.348** | 0.032 | **0.298** | 0.015 |

1. SMD before and after matching for the variables included in the propensity score, for the T2DM analysis set.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Other beta-blockers versus bisoprolol** | | **ACEi/ARB versus bisoprolol** | | **CCB versus bisoprolol** | | **Diuretics versus bisoprolol** | |
| **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** |
| **Age at index** | **0.197** | 0.035 | **0.358** | 0.060 | **0.384** | 0.026 | **0.401** | 0.042 |
| **Sex = MALE** | 0.027 | 0.017 | **0.162** | 0.016 | 0.040 | 0.039 | **0.221** | 0.020 |
| **Region at index** | **0.560** | 0.081 | **0.367** | 0.061 | **0.422** | 0.047 | **0.505** | 0.075 |
| **BMI at index** | 0.024 | 0.008 | **0.242** | 0.035 | 0.012 | 0.019 | 0.053 | 0.039 |
| **Systolic blood pressure at index** | **0.328** | 0.085 | 0.055 | 0.001 | **0.279** | 0.042 | **0.338** | 0.057 |
| **Diastolic blood pressure at index** | **0.373** | 0.098 | **0.254** | 0.027 | 0.021 | 0.010 | 0.041 | 0.008 |
| **Presence of myocardial infarction at baseline** | 0.097 | 0.002 | **0.125** | 0.005 | **0.141** | < 0.001 | **0.135** | 0.019 |
| **Presence of angina at baseline** | **0.138** | 0.046 | **0.265** | 0.051 | **0.256** | 0.001 | **0.248** | 0.031 |
| **Presence of arrhythmia at baseline** | **0.341** | 0.059 | **0.374** | 0.057 | **0.373** | 0.045 | **0.369** | 0.065 |
| **Presence of chronic heart failure at baseline** | 0.072 | 0.004 | 0.053 | 0.004 | 0.077 | 0.018 | 0.061 | 0.005 |
| **Presence of stroke at baseline** | 0.048 | 0.038 | 0.004 | 0.059 | 0.030 | 0.043 | 0.037 | 0.030 |
| **Presence of peripheral vascular disease at baseline** | 0.005 | 0.001 | 0.002 | 0.052 | 0.052 | 0.047 | 0.043 | 0.044 |
| **Presence of dyslipidemia at baseline** | **0.109** | 0.018 | 0.018 | 0.049 | 0.041 | 0.012 | 0.099 | 0.022 |
| **Presence of chronic renal failure at baseline** | **0.118** | 0.002 | 0.060 | 0.030 | 0.016 | 0.023 | 0.077 | 0.004 |
| **Presence of depression at baseline** | 0.032 | 0.003 | 0.018 | 0.030 | 0.074 | 0.007 | 0.012 | 0.026 |
| **Presence of erectile dysfunction at baseline** | 0.007 | 0.025 | 0.083 | 0.041 | 0.082 | 0.044 | 0.031 | 0.051 |
| **Presence of sleep apnea at baseline** | 0.003 | 0.009 | 0.029 | 0.024 | 0.016 | 0.021 | 0.005 | 0.004 |
| **Current smoker** | **0.101** | 0.001 | 0.088 | 0.047 | 0.036 | 0.026 | 0.059 | 0.031 |
| **Use (current or past) of anti-coagulant at baseline** | **0.192** | 0.012 | **0.169** | 0.033 | **0.163** | 0.007 | **0.167** | 0.024 |
| **Use of anti-depressant at baseline** | 0.056 | 0.030 | 0.038 | 0.019 | 0.078 | 0.003 | 0.090 | 0.006 |
| **Use of anti-psychotic at baseline** | 0.016 | 0.001 | 0.021 | 0.015 | 0.001 | 0.031 | 0.035 | 0.037 |
| **Use of medication(s) leading to hypertension at baseline** | 0.024 | 0.035 | 0.053 | 0.007 | 0.071 | 0.020 | 0.005 | 0.023 |
| **Use of medication(s) leading to hypotension at baseline** | **0.215** | 0.046 | **0.251** | 0.011 | **0.179** | 0.018 | **0.270** | 0.004 |
| **Use of platelet aggregation inhibitor at baseline** | **0.343** | 0.071 | **0.411** | 0.038 | **0.369** | 0.005 | **0.321** | 0.006 |

1. SMD before and after matching for the variables included in the propensity score, for the dyslipidemia analysis set.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Other beta-blockers versus bisoprolol** | | **ACEi/ARB versus bisoprolol** | | **CCB versus bisoprolol** | | **Diuretics versus bisoprolol** | |
| **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** |
| **Age at index** | **0.186** | 0.037 | **0.335** | 0.053 | **0.387** | 0.031 | **0.409** | 0.039 |
| **Sex = MALE** | 0.018 | 0.003 | **0.165** | 0.003 | 0.039 | 0.032 | **0.222** | 0.012 |
| **Region at index** | **0.571** | 0.076 | **0.391** | 0.054 | **0.437** | 0.042 | **0.519** | 0.074 |
| **BMI at index** | 0.030 | 0.002 | **0.275** | 0.031 | 0.003 | 0.025 | 0.045 | 0.008 |
| **Systolic blood pressure at index** | **0.321** | 0.047 | 0.025 | 0.007 | **0.269** | 0.026 | **0.328** | 0.052 |
| **Diastolic blood pressure at index** | **0.366** | 0.093 | **0.208** | 0.009 | 0.013 | 0.005 | 0.033 | 0.012 |
| **Presence of myocardial infarction at baseline** | 0.083 | 0.006 | **0.112** | 0.026 | **0.127** | 0.004 | **0.120** | 0.014 |
| **Presence of angina at baseline** | **0.131** | 0.032 | **0.249** | 0.052 | **0.240** | 0.011 | **0.232** | 0.019 |
| **Presence of arrhythmia at baseline** | **0.340** | 0.043 | **0.375** | 0.083 | **0.374** | 0.055 | **0.369** | 0.057 |
| **Presence of chronic heart failure at baseline** | 0.086 | 0.008 | 0.072 | 0.005 | 0.090 | 0.024 | 0.076 | 0.003 |
| **Presence of stroke at baseline** | 0.027 | 0.055 | 0.007 | 0.049 | 0.012 | 0.038 | 0.024 | 0.043 |
| **Presence of peripheral vascular disease at baseline** | 0.005 | 0.004 | 0.008 | 0.020 | 0.040 | 0.035 | 0.034 | 0.030 |
| **Presence of diabetes at baseline** | 0.042 | 0.035 | **0.331** | 0.007 | 0.027 | 0.011 | 0.057 | 0.020 |
| **Presence of chronic renal failure at baseline** | **0.115** | 0.020 | 0.053 | 0.056 | 0.016 | 0.024 | 0.074 | 0.018 |
| **Presence of depression at baseline** | 0.045 | 0.006 | 0.004 | 0.017 | 0.064 | 0.031 | 0.001 | 0.047 |
| **Presence of erectile dysfunction at baseline** | 0.007 | 0.017 | **0.102** | 0.016 | 0.083 | 0.044 | 0.028 | 0.047 |
| **Presence of sleep apnea at baseline** | 0.004 | 0.010 | 0.030 | < 0.001 | 0.016 | 0.018 | 0.008 | < 0.001 |
| **Current smoker** | **0.105** | 0.030 | 0.098 | 0.010 | 0.038 | 0.023 | 0.064 | 0.009 |
| **Use (current or past) of anti-coagulant at baseline** | **0.191** | 0.025 | **0.170** | 0.032 | **0.166** | 0.013 | **0.170** | 0.003 |
| **Use of anti-depressant at baseline** | 0.047 | 0.044 | 0.026 | 0.004 | 0.069 | 0.002 | 0.082 | 0.017 |
| **Use of anti-psychotic at baseline** | 0.014 | 0.040 | 0.025 | 0.025 | 0.004 | 0.003 | 0.030 | 0.037 |
| **Use of medication(s) leading to hypertension at baseline** | 0.025 | 0.039 | 0.051 | 0.014 | 0.072 | 0.005 | 0.004 | 0.027 |
| **Use of medication(s) leading to hypotension at baseline** | **0.214** | 0.024 | **0.238** | 0.015 | **0.171** | 0.019 | **0.265** | 0.012 |
| **Use of platelet aggregation inhibitor at baseline** | **0.326** | 0.060 | **0.355** | 0.030 | **0.348** | 0.016 | **0.300** | 0.024 |

1. SMD before and after matching for the variables included in the propensity score, for the obesity analysis set.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Other beta-blockers versus bisoprolol** | | **ACEi/ARB versus bisoprolol** | | **CCB versus bisoprolol** | | **Diuretics versus bisoprolol** | |
| **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** |
| **Age at index** | **0.194** | 0.064 | **0.310** | 0.058 | **0.392** | 0.027 | **0.417** | 0.055 |
| **Sex = MALE** | 0.027 | 0.004 | **0.181** | 0.005 | 0.041 | 0.016 | **0.208** | 0.017 |
| **Region at index** | **0.567** | 0.067 | **0.389** | 0.100 | **0.433** | 0.052 | **0.517** | 0.076 |
| **BMI at index** | **0.175** | 0.029 | **0.302** | 0.042 | **0.119** | 0.062 | 0.082 | 0.030 |
| **Systolic blood pressure at index** | **0.326** | 0.046 | 0.043 | 0.003 | **0.282** | 0.023 | **0.346** | 0.065 |
| **Diastolic blood pressure at index** | **0.385** | **0.103** | **0.219** | 0.045 | 0.025 | 0.011 | 0.051 | 0.004 |
| **Presence of myocardial infarction at baseline** | **0.105** | 0.002 | **0.131** | 0.025 | **0.149** | 0.019 | **0.144** | 0.020 |
| **Presence of angina at baseline** | **0.130** | 0.018 | **0.262** | 0.065 | **0.252** | 0.002 | **0.247** | 0.024 |
| **Presence of arrhythmia at baseline** | **0.327** | 0.067 | **0.363** | 0.095 | **0.365** | 0.057 | **0.360** | 0.067 |
| **Presence of chronic heart failure at baseline** | 0.080 | 0.053 | 0.060 | < 0.001 | 0.083 | 0.016 | 0.069 | 0.014 |
| **Presence of stroke at baseline** | 0.035 | 0.043 | 0.010 | 0.058 | 0.019 | 0.056 | 0.029 | 0.031 |
| **Presence of peripheral vascular disease at baseline** | 0.004 | 0.026 | 0.001 | 0.031 | 0.051 | 0.057 | 0.037 | 0.040 |
| **Presence of diabetes at baseline** | 0.045 | 0.014 | **0.285** | 0.020 | 0.011 | 0.039 | 0.063 | 0.010 |
| **Presence of dyslipidemia at baseline** | **0.103** | 0.032 | 0.013 | 0.043 | 0.030 | 0.003 | 0.095 | 0.001 |
| **Presence of chronic renal failure at baseline** | **0.125** | 0.006 | 0.061 | 0.025 | 0.009 | 0.016 | 0.084 | 0.012 |
| **Presence of depression at baseline** | 0.034 | 0.019 | 0.019 | 0.044 | 0.075 | 0.025 | 0.015 | 0.014 |
| **Presence of erectile dysfunction at baseline** | 0.003 | 0.021 | 0.091 | 0.064 | 0.074 | 0.059 | 0.021 | 0.056 |
| **Presence of sleep apnea at baseline** | 0.017 | 0.022 | 0.009 | < 0.001 | < 0.001 | 0.004 | 0.018 | 0.015 |
| **Current smoker** | 0.072 | 0.015 | 0.086 | 0.029 | 0.034 | 0.041 | 0.045 | 0.047 |
| **Use (current or past) of anti-coagulant at baseline** | **0.170** | < 0.001 | **0.145** | 0.047 | **0.144** | 0.002 | **0.144** | 0.019 |
| **Use of anti-depressant at baseline** | 0.055 | 0.020 | 0.052 | 0.029 | 0.080 | 0.018 | 0.097 | 0.014 |
| **Use of anti-psychotic at baseline** | 0.008 | 0.016 | 0.035 | 0.011 | 0.008 | 0.010 | 0.026 | 0.041 |
| **Use of medication(s) leading to hypertension at baseline** | 0.020 | 0.051 | 0.066 | 0.004 | 0.082 | 0.028 | 0.017 | 0.043 |
| **Use of medication(s) leading to hypotension at baseline** | **0.218** | 0.033 | **0.255** | 0.017 | **0.184** | 0.037 | **0.278** | 0.022 |
| **Use of platelet aggregation inhibitor at baseline** | **0.346** | 0.069 | **0.372** | 0.038 | **0.363** | 0.016 | **0.322** | 0.015 |

1. Standardized mean differences (SMD) before and after matching for the variables included in the propensity score, for the erectile dysfunction analysis set.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Other beta-blockers versus bisoprolol** | | **ACEi/ARB versus bisoprolol** | | **CCB versus bisoprolol** | | **Diuretics versus bisoprolol** | |
| **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** | **SMD before matching** | **SMD after matching** |
| **Age at index** | **0.142** | 0.007 | **0.292** | 0.041 | **0.414** | 0.070 | **0.451** | 0.045 |
| **Region at index** | **0.575** | **0.104** | **0.383** | 0.089 | **0.442** | 0.051 | **0.502** | 0.097 |
| **BMI at index** | 0.057 | 0.040 | **0.167** | 0.016 | 0.095 | 0.068 | **0.192** | 0.040 |
| **Systolic blood pressure at index** | **0.363** | 0.045 | 0.054 | 0.015 | **0.291** | 0.016 | **0.341** | 0.036 |
| **Diastolic blood pressure at index** | **0.358** | 0.035 | **0.174** | 0.024 | 0.009 | 0.011 | 0.015 | 0.018 |
| **Presence of myocardial infarction at baseline** | **0.101** | 0.003 | **0.146** | 0.026 | **0.160** | 0.042 | **0.151** | 0.021 |
| **Presence of angina at baseline** | **0.172** | 0.034 | **0.314** | 0.087 | **0.305** | 0.057 | **0.297** | 0.064 |
| **Presence of arrhythmia at baseline** | **0.347** | 0.064 | **0.389** | 0.053 | **0.386** | 0.088 | **0.379** | 0.083 |
| **Presence of chronic heart failure at baseline** | 0.087 | 0.006 | 0.075 | 0.004 | 0.095 | 0.006 | 0.078 | 0.027 |
| **Presence of stroke at baseline** | 0.012 | 0.091 | 0.024 | 0.052 | 0.004 | 0.084 | 0.017 | 0.068 |
| **Presence of peripheral vascular disease at baseline** | 0.010 | 0.063 | 0.013 | 0.066 | 0.078 | 0.081 | 0.062 | 0.065 |
| **Presence of diabetes at baseline** | 0.055 | 0.004 | **0.348** | 0.052 | 0.020 | 0.080 | 0.058 | 0.021 |
| **Presence of chronic renal failure at baseline** | 0.088 | 0.051 | 0.065 | 0.045 | 0.045 | 0.036 | 0.043 | 0.025 |
| **Presence of depression at baseline** | 0.002 | 0.028 | 0.049 | 0.044 | 0.095 | 0.037 | 0.063 | 0.039 |
| **Presence of dyslipidemia at baseline** | 0.080 | 0.020 | 0.028 | 0.035 | 0.035 | 0.015 | 0.094 | 0.034 |
| **Presence of sleep apnea at baseline** | 0.017 | 0.022 | 0.047 | 0.036 | 0.037 | 0.055 | 0.013 | 0.008 |
| **Current smoker** | **0.102** | 0.039 | 0.070 | 0.014 | 0.035 | 0.055 | 0.062 | 0.054 |
| **Use (current or past) of anti-coagulant at baseline** | **0.201** | 0.017 | **0.192** | 0.017 | **0.183** | < 0.001 | **0.175** | 0.020 |
| **Use of anti-depressant at baseline** | 0.025 | 0.032 | 0.011 | 0.014 | 0.046 | 0.034 | 0.082 | 0.006 |
| **Use of anti-psychotic at baseline** | 0.011 | 0.011 | 0.040 | 0.008 | 0.020 | 0.014 | 0.008 | 0.029 |
| **Use of medication(s) leading to hypertension at baseline** | 0.002 | 0.047 | 0.030 | 0.027 | 0.011 | 0.034 | 0.040 | 0.012 |
| **Use of medication(s) leading to hypotension at baseline** | **0.290** | 0.024 | **0.344** | 0.001 | **0.241** | 0.013 | **0.331** | 0.009 |
| **Use of platelet aggregation inhibitor at baseline** | **0.396** | 0.077 | **0.441** | 0.041 | **0.428** | 0.048 | **0.352** | 0.003 |

Supplementary Table 6. Transition intensities for the multi-state model between controlled and uncontrolled BP states, length of stay in the controlled state, after matching in the BP analysis set.

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment | PS-matched HR  (CI 98.75%)  Uncontrolled to controlled BP | PS-matched HR  (CI 98.75%)  Controlled to uncontrolled BP | Mean length of stay (CI 98.75%) in the controlled BP state, months |
| Bisoprolol vs  other beta-blockers | 0.97 (0.89, 1.05) | 1.12 (1.02, 1.22) | 21.55 (19.76, 23.38)  20.07 (19.27, 20.92) |
| Bisoprolol vs ACEi/ARB | 1.05 (0.98, 1.13) | 1.10 (1.01, 1.19) | 22.03 (20.41, 23.91)  24.48 (23.59, 25.33) |
| Bisoprolol vs  CCB | 0.94 (0.87, 1.01) | 0.99 (0.91, 1.08) | 21.62 (19.97, 23.50)  19.97 (19.20, 20.80) |
| Bisoprolol vs diuretics | 0.92 (0.85, 0.99) | 1.19 (1.10, 1.30) | 21.98 (20.50, 23.58)  18.81 (18.10, 19.54) |

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BP, blood pressure; CCB, calcium channel blockers; HR, hazard ratio

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Event of interest** | **Number of patients in each comparison group** | | | **Number of events** | | **PS-matched incidence rates per 1,000 person-years (98.75% CI)** | |
|  | **Bisoprolol** | **Comparator** | **Bisoprolol** | | **Comparator** | **Bisoprolol** | **Comparator** |
| **T2DM** |  |  |  | |  |  |  |
| Bisoprolol vs other beta-blockers | 1,640 | 6,560 | 41 | | 154 | 0.04 (0.02, 0.05) | 0.04 (0.03, 0.04) |
| Bisoprolol vs ACEi/ARB | 1,929 | 7,716 | 45 | | 313 | 0.03 (0.02, 0.05) | 0.05 (0.04, 0.05) |
| Bisoprolol vs CCB | 1,881 | 7,524 | 44 | | 175 | 0.03 (0.02, 0.05) | 0.04 (0.03, 0.04) |
| Bisoprolol vs diuretics | 1,804 | 7,216 | 43 | | 165 | 0.03 (0.02, 0.05) | 0.04 (0.03, 0.05) |
| **Dyslipidemia** |  |  |  | |  |  |  |
| Bisoprolol vs other beta-blockers | 1,577 | 6,308 | 100 | | 315 | 0.10 (0.08, 0.13) | 0.09 (0.08, 0.10) |
| Bisoprolol vs ACEi/ARB | 1,810 | 7,240 | 127 | | 671 | 0.11 (0.09, 0.14) | 0.11 (0.10, 0.12) |
| Bisoprolol vs CCB | 1,788 | 7,152 | 127 | | 395 | 0.11 (0.09, 0.14) | 0.09 (0.08, 0.11) |
| Bisoprolol vs diuretics | 1,721 | 6,884 | 121 | | 320 | 0.11 (0.09, 0.14) | 0.08 (0.07, 0.10) |
| **Obesity** |  |  |  | |  |  |  |
| Bisoprolol vs other beta-blockers | 1,424 | 5,696 | 83 | | 290 | 0.09 (0.07, 0.12) | 0.08 (0.07, 0.09) |
| Bisoprolol vs ACEi/ARB | 1,612 | 6,448 | 93 | | 412 | 0.09 (0.07, 0.11) | 0.08 (0.07, 0.09) |
| Bisoprolol vs CCB | 1,609 | 6,436 | 103 | | 2,479 | 0.09 (0.07, 0.11) | 0.07 (0.06, 0.07) |
| Bisoprolol vs diuretics | 1,524 | 6,096 | 89 | | 271 | 0.09 (0.07, 0.11) | 0.08 (0.07, 0.09) |
| **Erectile dysfunction** |  |  |  | |  |  |  |
| Bisoprolol vs other beta-blockers | 879 | 3,516 | 6 | | 19 | 0.010 (0.003, 0.025) | 0.008 (0.004, 0.014) |
| Bisoprolol vs ACEi/ARB | 999 | 3,996 | 6 | | 55 | 0.009 (0.002, 0.022) | 0.015 (0.011, 0.021) |
| Bisoprolol vs CCB | 934 | 3,736 | 6 | | 46 | 0.009 (0.002, 0.023) | 0.020 (0.013, 0.028) |
| Bisoprolol vs diuretics | 896 | 3,584 | 6 | | 22 | 0.009 (0.003, 0.024) | 0.012 (0.007, 0.020) |

Supplementary Table 7. Number of events and safety event incidence rates after matching, for each event of interest and comparison group.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; CI, confidence interval; PS, propensity score; T2DM, type 2 diabetes.

Supplementary Table 8. Cause-specific Cox proportional hazards models and Fine and Gray models for T2DM – sensitivity analysis excluding patients with prior impaired fasting blood glucose levels.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio; T2DM, type 2 diabetes

|  |  |  |
| --- | --- | --- |
| Comparison groups in T2DM analysis set | HR (98.75% CI) | SHR (98.75% CI) |
| Other beta-blockers vs bisoprolol | 0.99 (0.62, 1.56) | 0.94 (0.59, 1.48) |
| ACEi/ARB vs bisoprolol | 1.59 (1.05, 2.42) | 1.87 (1.23, 2.83) |
| CCB vs bisoprolol | 1.17 (0.76, 1.81) | 1.11 (0.72, 1.70) |
| Diuretics vs bisoprolol | 1.04 (0.66, 1.65) | 0.88 (0.56, 1.40) |

Supplementary Table 9. Cause-specific Cox proportional hazards models and Fine and Gray models for competing events of outcome for interest.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TD2M** | | **Dyslipidemia** | | **Erectile dysfunction** | | **Obesity** | |
|  | **HR (98.75% CI)** | **SHR (98.75% CI)** | **HR (98.75% CI)** | **SHR (98.75% CI)** | **HR (98.75% CI)** | **SHR (98.75% CI)** | **HR (98.75% CI)** | **SHR (98.75% CI)** |
| **Other Beta-Blockers**  **vs bisoprolol** | 1.05 (0.98, 1.12) | 1.06 (0.99, 1.13) | 1.07 (1.00, 1.15) | 1.10 (1.02, 1.18) | 1.06 (0.96, 1.16) | 1.06 (0.97, 1.16) | 1.05 (0.97, 1.12) | 1.07 (0.99, 1.15) |
|  |  |  |  |  |  |  |  |  |
| **ACEi/ARB**  **vs bisoprolol** | 0.82 (0.77, 0.88) | 0.80 (0.75, 0.86) | 0.78 (0.72, 0.84) | 0.80 (0.75, 0.86) | 0.81 (0.74, 0.89) | 0.80 (0.73, 0.87) | 0.83 (0.77, 0.90) | 0.85 (0.79, 0.92) |
|  |  |  |  |  |  |  |  |  |
| **CCB**  **vs bisoprolol** | 1.06 (0.99, 1.13) | 1.04 (0.98, 1.11) | 1.06 (0.99, 1.13) | 1.07 (1.00, 1.14) | 1.07 (0.98, 1.18) | 1.04 (0.95, 1.13) | 1.05 (0.98, 1.13) | 1.04 (0.97, 1.11) |
|  |  |  |  |  |  |  |  |  |
| **Diuretics**  **vs bisoprolol** | 1.18 (1.11, 1.26) | 1.16 (1.09, 1.24) | 1.14 (1.06, 1.21) | 1.18 (1.11, 1.26) | 1.29 (1.18, 1.40) | 1.26 (1.16, 1.37) | 1.17 (1.09, 1.25) | 1.17 (1.09, 1.25) |

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio; T2DM, type 2 diabetes; SHR, sub-distribution hazard ratio.

# Supplementary Appendix B

Supplementary Appendix B. Variables definitions, READ code and product code lists.