# Fixed-dose combination antihypertensives and risk of medication errors

Frank Moriarty1

Kathleen Bennett2

Tom Fahey1

1 HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, 123 Stephen’s Green, Dublin 2

2 Division of Population Health Sciences, Royal College of Surgeons in Ireland, Beaux Lane House, Dublin 2

**Table S1 Antihypertensive fixed-dose combinations with equivalent free components available during 2015 and included in this study**

|  |  |
| --- | --- |
| **Antihypertensive class** | **Available fixed-dose combinations** |
| ACE inhibitors | Enalapril, lercanidipine  Perindopril, amlodipine  Perindopril, indapamide, amlodipine  Ramipril, felodipine |
| Angiotensin receptor II blockers | Valsartan, amlodipine  Valsartan, hydrochlorothiazide, amlodipine  Olmesartan, amlodipine  Olmesartan, hydrochlorothiazide, amlodipine  Telmisartan, amlodipine |
| Beta blockers | Atenolol, nifedipine |

**Table S2 Class-specific drug-drug interactions (DDI) considered as potentially serious by the British National Formulary relating to antihypertensive drug classes**

|  |  |  |
| --- | --- | --- |
|  | **Interacting drugs/drug classes** | **Hypotension-only interactions** |
| **ACE inhibitors** | Aliskiren  Amiloride  Angiotensin II receptor blockers Ciclosporin  Eplerenone  Everolimus  Lithium  Potassium canrenoate/salts  Sacubitril  Spironolcatone  Triamterene | Diuretics |
| **Angiotensin II receptor blockers** | ACE inhibitors  Alsikiren  Amiloride  Ciclosporin  Eplerenone  Lithium  Potassium canrenoate/salts  Spironolcatone  Triamterene | Diuretics |
| **Beta blockers** | Adrenaline  Amiodarone  Anti-arrhythmics (including flecainide)  Clonidine  Diltiazem  Dobutamine  Fingolimod  Noradrenaline | Adrenaline  Alpha blockers  Moxisylyte  Nifedipine  Noradrenaline  Verapamil |
| **Calcium channel blockers** | Aminophylline  Clarithromycin  Erythromycin  Phenobarbital  Primidone  Ritonavir  Theophylline  Simvastatina  Itraconazoleb  Ketoconazoleb  Ciclosporinc  Digoxinc,d  Beta blockersd  Dronedaroned  Rifampicind  Tacrolimusd | Alpha adrenergic blockers  Magnesium (parenteral)d |

Interaction specific to aamlodipine, bfelodipine, clercanidipine, dnifedipine

**Table S3 Prevalence of individual drug-drug interactions**

|  |  |  |  |
| --- | --- | --- | --- |
| **Antihypertensives and interacting agents** | **n** | **% by class** | **% overall** |
| **Angiotensin II receptor blockers** | **13,611** | **100** | **27.96** |
| ACE inhibitors | 6,938 | 50.97 | 14.25 |
| Alsikiren | 851 | 6.25 | 1.75 |
| Amiloride | 9 | 0.07 | 0.02 |
| Eplerenone | 678 | 4.98 | 1.39 |
| Lithium | 677 | 4.97 | 1.39 |
| Potassium | 3,965 | 29.13 | 8.14 |
| Spironolactone | 1,749 | 12.85 | 3.59 |
| **ACE inhibitors** | **12,737** | **100** | **26.16** |
| Alsikiren | 321 | 2.52 | 0.66 |
| Amiloride | 13 | 0.10 | 0.03 |
| ARB | 7,031 | 55.20 | 14.44 |
| Ciclosporin | 11 | 0.09 | 0.02 |
| Eplerenone | 407 | 3.20 | 0.84 |
| Lithium | 530 | 4.16 | 1.09 |
| Potassium | 4,149 | 32.57 | 8.52 |
| Spironolactone | 971 | 7.62 | 1.99 |
| **Beta blockers** | **121** | **100** | **0.25** |
| Amiodarone | 29 | 23.97 | 0.06 |
| Anti-arrhythmics (including flecainide) | 50 | 41.32 | 0.10 |
| Clonidine | 31 | 25.62 | 0.06 |
| Diltiazem | 40 | 33.06 | 0.08 |
| **Calcium channel blockers** | **29,153** | **100** | **59.88** |
| Amlodipine |  |  |  |
| Theophylline/aminophylline | 1,933 | 6.63 | 3.97 |
| Macrolides | 534 | 1.83 | 1.10 |
| Barbituates | 700 | 2.40 | 1.44 |
| Simvastatin | 19,725 | 67.66 | 40.51 |
| Lercanidipine |  |  |  |
| Theophylline/aminophylline | 68 | 0.23 | 0.14 |
| Macrolides | 9 | 0.03 | 0.02 |
| Felodipine |  |  |  |
| Theophylline/aminophylline | 151 | 0.52 | 0.31 |
| Macrolides | 16 | 0.05 | 0.03 |
| Barbituates | 32 | 0.11 | 0.07 |
| Itraconazole/ketoconazole | 1 | <0.01 | <0.01 |
| Nifedipine |  |  |  |
| Theophylline/aminophylline | 38 | 0.13 | 0.08 |
| Macrolides | 4 | 0.01 | 0.01 |
| Digoxin | 58 | 0.20 | 0.12 |
| Beta blockers | 6,168 | 21.16 | 12.67 |

**Table S4 Descriptive statistics of propensity-matched cohort with standardised mean differences before and after matching**

|  |  |  |  |
| --- | --- | --- | --- |
|  | FC | FDC | SMD post-matching |
| **Number of prescriptions** | 146,813 | 146,813 |  |
| **Patient age (years)**  Mean (SD) | 70.0 (12.0) | 69.9 (11.9) | <0.001 |
| **Female**, n (%) | 70,648 (48.1) | 71,135 (48.5) | 0.014 |
| **Antihypertensive type**b, n (%) |  |  |  |
| Beta blocker | 1,317 (0.9) | 1,256 (0.9) | 0.048 |
| ACE inhibitor (+/- beta blocker) | 68.294 (46.5) | 62,921 (42.9) | 0.148 |
| ARB (+/- beta blocker or ACE inhibitor) | 77,202 (55.6) | 82,636 (56.3)\*\*\* | 0.149 |
| **Total number of antihypertensive DDDs prescribed**  Mean (SD) | 88.0 (31.0) | 89.7 (26.5) \*\*\* | 0.020 |
| **Any other BP drugs**, n (%) | 63874 (44.5) | 69914 (45.6) \*\*\* | 0.064 |
| **Any other CV drug**, n (%) | 8461 (5.8) | 9384 (6.4) \*\*\* | 0.074 |
| **Any antiplatelet/anticoagulant**, n (%) | 69390 (47.3) | 71437 (48.7) \*\*\* | 0.054 |
| **Any cholesterol drug**, n (%) | 79479 (54.1) | 83286 (56.7) \*\*\* | 0.102 |
| **Any diabetic drug**, n (%) | 17112 (11.7) | 18226 (12.4) \*\*\* | 0.048 |
| **Number of other items on prescription**  Median (IQR) | 2 (1-4) | 2 (1-4) \*\*\* | 0.038 |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CV, cardiovascular drug; FC, free combination; FDC, fixed-dose combination; SMD, standardised mean difference.

**Table S5 Additional sensitivity analyses using propensity score adjustment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Duplicate** |  | **Drug interaction** |  |
|  | **Relative risk**  **(95% CI)** | **P value** | **Relative risk**  **(95% CI)** | **P value** |
| PS matched regressiona, adjusting for all covariates | 2.17 (1.72, 2.74) | <0.001 | 1.04 (0.98, 1.10) | 0.165 |
| PS matched regression, trimming at 2.5th, 97.5th percentile | 2.32 (1.82, 2.96) | <0.001 | 1.09 (1.02, 1.16) | 0.007 |
| As above, adjusting for all covariates | 2.17 (1.70, 2.77) | <0.001 | 1.03 (0.97, 1.10) | 0.310 |
| Adjusted for PS | 2.20 (1.73, 2.80) | <0.001 | 1.00 (0.95, 1.06) | 0.919 |
| Adjusting for PS and all covariates | 2.10 (1.67, 2.65) | <0.001 | 1.00 (0.94, 1.05) | 0.942 |
| Adjusting for quintiles of PS | 2.04 (1.62, 2.56) | <0.001 | 0.88 (0.83, 0.93) | <0.001 |
| Adjusting for quintiles of PS and all covariates | 2.09 (1.66, 2.63) | <0.001 | 1.00 (0.95, 1.06) | 0.890 |
| Adjusting for quintiles of PS, trimming at 2.5th, 97.5th percentile | 2.09 (1.64, 2.66) | <0.001 | 1.00 (0.94, 1.06) | 0.891 |
| As above, and adjusted for all covariates | 2.09 (1.65, 2.66) | <0.001 | 0.99 (0.94, 1.05) | 0.781 |

a Propensity score generated from logit model including: patient age and gender, type of combination product (ARB, ACE inhibitor or beta blocker), and total number of antihypertensive DDDs in the FC/FDC, number of other antihypertensive prescription items, number of other cardiovascular drugs, number of antiplatelet/anticoagulant drugs, number of cholesterol drugs, number of diabetes drugs, and number of other prescribed items.



**Figure S1 Propensity scores distributions pre- and post-matching, with quintiles shown.**