Received: 13 April 2023 | Revised: 6 November 2023 | Accepted: 9 November 2023

DOI: 10.1002/pds.5730

ORIGINAL ARTICLE

WILEY

Drug-induced orthostatic hypotension: Cluster analysis of co-prescription patterns in older people in UK primary care

Cini Bhanu[1] | Irene Petersen[1] | Mine Orlu[2] | Daniel Davis[3] | Reecha Sofat[4,5] | Juan Carlos Bazo-Alvarez[1] | Kate Walters[1]

[1]Research Department of Primary Care and Population Health, University College London, London, UK

[2]University College London (UCL) School of Pharmacy, UK

[3]MRC Unit for Lifelong Health & Ageing, University College London, London, UK

[4]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

[5]British Heart Foundation, Data Science Centre, UK

Correspondence
Cini Bhanu, Centre for Ageing Population Studies, Research department of Primary Care and Population Health, University College London (UCL), London NW3 2PF, UK.
Email: c.bhanu@ucl.ac.uk

Funding information
Dunhill Medical Trust

Abstract

Purpose: Over 250 medications are reported to cause orthostatic hypotension, associated with serious adverse outcomes in older adults. Studies suggest a harmful cumulative risk of orthostatic hypotension with multiple medication use. However, there is limited evidence on the potential for harm in practice, particularly which drugs is co-prescribed and may increase risk of orthostatic hypotension.

Methods: Retrospective cohort study and cluster analysis using general practice data from IQVIA Medical Research Data (IMRD) in patients aged ≥50 contributing data between 1 January 2018 and 31 December 2018. Thirteen drug groups known to be associated with orthostatic hypotension by mechanism, were analyzed and clusters generated by sex and age-band.

Results: A total of 602 713 individuals aged ≥50 with 283 912 (47%) men and 318 801 (53%) women were included. The most prevalent prescriptions that might contribute to orthostatic hypotension were ACE inhibitors, calcium-channel blockers, beta-blockers, selective serotonin reuptake inhibitors and uroselective alpha-blockers. We identified distinct clusters of cardiovascular system (cardiovascular system) drugs in men and women at all ages. cardiovascular system plus psychoactive drug clusters were common in women at all ages, and in men aged ≤70. cardiovascular system plus uroselective alpha-blockers were identified in men aged ≥70.

Conclusions: Distinct clusters of drugs associated with orthostatic hypotension exist in practice, which change over the life course. Our findings highlight potentially harmful drug combinations that may cause cumulative risk of orthostatic hypotension in older people. This may guide clinicians about the potential of synergistic harm and to monitor for orthostatic hypotension if using combinations of cardiovascular system drugs, cardiovascular system plus psychoactive drugs and/or alpha-blockers—particularly in patients aged ≥70 or at high-risk due to comorbidity. Future research should consider quantifying the risk of drug-induced orthostatic hypotension with such drug combinations.

KEYWORDS
ageing, orthostatic hypotension, polypharmacy, postural hypotension

Key Points

- Drug-induced orthostatic hypotension is common amongst older adults—over 250 drugs are potentially causative and the risk increases with combined drug use.
- This study has identified clusters of co-prescriptions that are potentially associated with high risk of orthostatic hypotension.
- Common clusters of drugs associated with adverse orthostatic hypotension include: combinations of cardiovascular system (cardiovascular system) drugs (e.g. antihypertensives); cardiovascular system drugs + psychoactive drugs (e.g. antidepressants); and cardiovascular system drugs + uroselective alpha-blockers in men (e.g. tamsulosin).
- Clinicians should be aware of the potential for synergistic harm with such drug combinations in practice and to monitor for orthostatic hypotension—particularly in patients aged ≥70 or at high-risk due to comorbidity.
- Future research should consider quantifying the risk and harms of drug-induced orthostatic hypotension with such drug combinations.

Plain Language Summary

Orthostatic hypotension (orthostatic hypotension) is a common condition amongst older adults characterized by a temporary drop in blood pressure on standing upright. It is associated with numerous adverse outcomes including a greater risk of fall, strokes, heart attacks and dementia in older people. Drugs are the commonest cause of orthostatic hypotension in older people, and the use of multiple drugs in combination can increase the risk of orthostatic hypotension. We studied prescription patterns in an older population using UK general practice data. We identified clusters of drugs associated with orthostatic hypotension that are commonly prescribed together, and therefore likely to result in high-risk of orthostatic hypotension. These clusters include combination of blood pressure lowering drugs; blood pressure lowering drugs plus antidepressants; and blood pressure lowering drugs plus drugs used for urinary symptoms in men. Prescribers should be aware of the increased risk of orthostatic hypotension with these combinations and should consider screening for orthostatic hypotension in patients if using them. Future research should explore these combinations further to quantify the risk of orthostatic hypotension and associated harms in older people.

1 | INTRODUCTION

Orthostatic hypotension (orthostatic hypotension), defined as a reduction in systolic blood pressure (BP) of ≥20 mm Hg or diastolic BP of ≥10 mm Hg within 3 min of assuming an erect posture,[1] is common in older people and often caused by medications.[2,3] It is associated with serious adverse outcomes in later life, including falls,[4] ischaemic coronary events,[2] strokes[5] and cognitive impairment.[6] Causes of orthostatic hypotension are neurogenic (inherent structural lesions of autonomic pathways, for example, Parkinson disease) or non-neurogenic (non-inherent, functional causes of autonomic failure). Among the latter, medications are the most typical cause.[3] Over 250 medications are reported to cause orthostatic hypotension.[7] There is an increased risk of orthostatic hypotension with combinations of drugs causing a cumulative effect[2–7 8]. Recent guidelines warn about the synergistic effect of multiple medications causing orthostatic hypotension in older adults with polypharmacy.[9]

Recent studies have identified drug groups associated with orthostatic hypotension, including cardiovascular drugs (such as beta-blockers and certain antihypertensives), psychoactive drugs (such as tricyclic antidepressants and antipsychotics) and uroselective alpha blockers,[3,10] among others. However, there is limited evidence on the potential for harm with current practice, including which drugs are commonly co-prescribed that may increase risk of orthostatic hypotension. Previous studies have described common co-prescriptions, or "clusters" of drugs among older adults with multimorbidity.[11] However, none describe common drug combinations associated explicitly with orthostatic hypotension. This study aims to (i) examine the prevalence of common drug groups associated with orthostatic hypotension in electronic health records and (ii) to describe the clusters of co-prescriptions associated with orthostatic hypotension by sex and age-band. This information would highlight potentially harmful co-prescriptions and guide more targeted risk assessment and screening for drug-induced orthostatic hypotension.

2 | METHODS

2.1 | Design

Retrospective cohort study and cluster analysis using routinely collected health-care data.

2.2 | Data source

This study used general practice data from anonymized electronic healthcare records contributing to IQVIA medical research data (IMRD), which includes over 18 million patients from over 750 general practices.[12] These broadly represent UK practices regarding age, sex, practice size, geographical distribution and socio-demographic characteristics.[13]

In the UK, health-care access is free and individuals typically register with a General Practitioner (GP) in their local area. Approximately, 98% of the UK populations are registered with a GP[14] and over 90% of NHS contacts are in general practice.[15] During routine healthcare, GPs record patient information (such as symptoms, diagnoses, examination results, measurements and prescriptions). Most information is systematically recorded using the Read classification coding system.[16] In the UK, GPs often use the British National Formulary (BNF) to guide prescribing.[17] Prescription data are coded automatically when entered and are essentially complete (though this does not include drugs bought over the counter without a prescription). Prescription data can be linked to diagnoses and other clinical information.[18]

Social deprivation is measured using linked population census data on the Townsend score (based on postcode sector area of residence, owner-occupation, car ownership, overcrowding and unemployment).[19] This is split into quintiles 1–5 (1 being the least deprived).

2.3 | Study population

The source population was all patients aged at least 50 years, registered with a GP practice contributing data to IMRD at acceptable quality and mortality reporting levels[20,21] for at least one full year between January 1, 2018 and December 31, 2018. The demographics of the individuals were stratified by sex, age (in 10-year age bands) and quintiles of Townsend score.

2.4 | Prescription data

We chose 13 drug groups associated with orthostatic hypotension based on a recent systematic review of randomized controlled trials (RCTs).[10] These groups were identified by mechanism in IMRD using British National Formulary (BNF) sub-chapter codes (Table 1).[17]

2.5 | Statistical analysis

We chose to use a cluster analysis method. Cluster analysis uses a data-driven approach to identify naturally emergent groups in a dataset, in order to generate hypotheses. It separates entities based on a measure of dissimilarity into distinct clusters.[22] This cluster analysis approach (in contrast to purely examining co-prescription prevalence) is a highly data-driven, exploratory method that identifies where natural groupings (or clusters) may lie in data, where there are not any pre-determined hypotheses.[22] It is also a more practical method for evaluating multiple medication combinations.[22]

Prescription data were converted into a binary format (i.e., whether a person had been prescribed a drug from each drug group in 2018 or not). A hierarchical clustering with Gower's dissimilarity measure for binary data and a Ward linkage method was used. Gower's dissimilarity measure quantifies dissimilarity between subjects with mixed non-numeric and numeric data.[23] It was chosen because it can consider large amounts of prescription data intrinsically dependent on each other (due to multiple comorbidities).[24] Clusters were generated by sex for the following age-bands: 50–59; 60–69; 70–79, and ≥ 80 years to investigate distinct higher-level clusters of two or three drug combinations based on prescription prevalence. Therefore, clusters of two or three medications indicate those that were most commonly co-prescribed in this population. Overall, the most prevalent co-prescription combinations were more likely to feature in the final clusters generated. The clusters were graphically visualized with hierarchical dendrograms by sex and age-band. All analyses were carried out using Stata 17.0.

TABLE 1 British National Formulary sub-chapter codes used in this study.

Chapter 2: Cardiovascular system
2.4. Beta-adrenoceptor blocking drugs (beta-blocker) (e.g., *bisoprolol)*
2.5.2. Centrally-acting antihypertensive drugs (alpha-agonist) (e.g., *clonidine)*
2.5.4. Alpha-adrenoceptor blocking drugs (alpha-blocker) (e.g., *doxazosin)*
2.5.5.1. Angiotensin converting enzyme (ACE) inhibitors (e.g., *ramipril)*
2.5.5.2. Angiotensin II receptor antagonists (e.g., *losartan)*
2.6.1. Nitrates (e.g., *glyceryl trinitrate)*
2.6.2. Calcium-channel blockers (CCB) (e.g., *amlodipine)*
Chapter 4: Central nervous system
4.2.1. Antipsychotic (AP) drugs (e.g., *risperidone)*
4.2.2. Antipsychotic (AP) depot injections
4.3.1. Tricyclic and related antidepressant drugs (e.g., *amitriptyline)*
4.3.3. Selective serotonin re-uptake inhibitors (SSRI) (e.g., *sertraline)*
Chapter 6: Endocrine system
6.1.2.3. Other antidiabetics (includes SGLT2 inhibitors) (e.g., *dapagliflozin)*
Chapter 7: Obstetrics, gynaecology and urinary-tract disorders
7.4.1. Drugs for urinary retention (e.g., *tamsulosin, alfuzosin)*

Abbreviations: *ACE, angitotensin converting enzyme; ARB, Angiotensin II receptor blocker; SGLT2: sodium-glucose cotransporter-2; SSRI: selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant*.

2.6 | Patient and public involvement

A patient and public involvement (PPI) advisory group of three older adults (two with experience of polypharmacy and one with experience of caring for an older adult with polypharmacy) contributed to our discussions of potential implications of our findings.

3 | RESULTS

In total, 602 713 people aged over 50 years contributed a full year of data to IMRD in 2018. (Table 2). The population included 283 912 (47.1%) men and 318 801 (52.9%) women. Overall, the women were older than the men (31.4% of women were above 80 years and 26% of men were above 80 years) (Table 2). The most prevalent prescriptions were cardiovascular system (cardiovascular system) drugs including angiotensin converting enzyme (ACE)-inhibitors, calcium-channel blockers (CCBs) and beta-blockers (Table 2). Selective serotonin reuptake inhibitors (SSRIs) were highly prevalent among women (21.2%) while 11.2% of men were prescribed SSRIs (Table 2). In contrast, uro-selective alpha-blockers were commonly prescribed in men (18.1%) but not in women.

The cluster analysis revealed some distinctive clusters of medication (Figure 1). In order to interpret the dendrogram, follow the diagram from top to bottom to identify the groupings. The drugs which are joined together lower in the diagram are more similar (and therefore more likely to be co-prescribed) than those connected at a higher level.

In men, clear clusters of cardiovascular system (cardiovascular system) drugs were evident at every age-band. Under 70 years, psychoactive drugs (such as SSRIs and TCAs) mostly cluster with antihypertensives. Over 70 years, uro-selective alpha-blockers cluster with antihypertensives. In women, distinct clusters of cardiovascular system and psychoactive drugs are seen at every age-band. SSRIs are also present at all ages, though clear clustering with ARBs is seen from ≥70 years.

TABLE 2 Patient demographics (2018); prevalence of prescriptions associated with orthostatic hypotension.

	Men (%)	Women (%)
Overall	**283 912 (47.1)**	**318 801 (52.9)**
Age-band, years		
50–59	31 037 (10.9)	37 000 (11.6)
60–69	86 986 (30.6)	88 632 (27.8)
70–79	92 195 (32.5)	93 027 (29.2)
80+	73 694 (26.0)	100 142 (31.4)
Townsend quintile		
1	59 667 (21.0)	62 994 (19.8)
2	59 098 (20.8)	64 523 (20.2)
3	55 462 (19.5)	63 176 (19.8)
4	45 295 (16.0)	54 368 (17.1)
5	32 014 (11.3)	38 027 (11.9)
Missing	32 376 (11.4)	35 713 (11.2)
Drug group (%)		
Cardiovascular system		
Beta-blocker	77 168 (26.7)	73 295 (23.0)
Alpha-agonist	745 (0.26)	998 (0.3)
Alpha-blocker	6566 (2.3)	5478 (1.7)
ACE-inhibitor	102 732 (36.2)	77 833 (24.1)
ARB	38 273 (13.5)	44 818 (14.1)
Nitrate	24 279 (8.6)	17 464 (5.5)
Calcium-channel blocker	91 646 (32.3)	85 312 (26.8)
Central nervous system		
Antipsychotic	7788 (2.7)	10 392 (3.3)
Antipsychotic depot	229 (0.1)	232 (0.1)
TCA	23 121 (8.1)	48 067 (15.1)
SSRI	31 770 (11.2)	67 663 (21.2)
Endocrine system		
SGLT-2 inhibitor	17 692 (6.2)	11 783 (3.7)
Obstetrics, gynaecology and urinary-tract disorders		
Uroselective alpha-blocker	51 289 (18.1)	7974 (2.5)

Abbreviations: ACE, angitotensin converting enzyme; ARB, Angiotensin II receptor blocker; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SGLT2, sodium-glucose cotransporter-2.

3.1 | 50–59 years

In men, two distinct clusters of drugs were prescribed: an antihypertensive cluster (ACE-inhibitor plus CCB); and cardiovascular system plus psychoactive drugs (beta-blocker plus TCA/SSRI). Women had a similar prescription pattern but one large cluster of cardiovascular system and psychoactive drugs. SSRIs were significant in women, but did not cluster with other drugs.

3.2 | 60–69 years

In men, there were two distinct clusters: a cardiovascular system cluster (beta-blocker, ACE-inhibitor and CCB); and an antihypertensive plus antidepressant (ARB plus SSRI). In contrast, women had one cluster of CVD and psychoactive drugs in combination (beta-blocker, ARB and TCA).

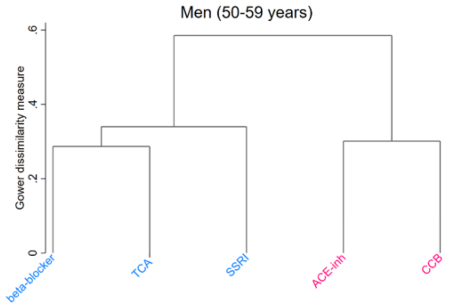
3.3 | 70–79 years

In men, the clusters remained similar to those aged 60–69 years. There was a consistent cardiovascular system drug cluster (beta-blocker, ACE-inhibitor and CCB). However, the second new cluster emerged: antihypertensive plus uro-selective alpha-blocker. The psychoactive drugs were no longer featured.

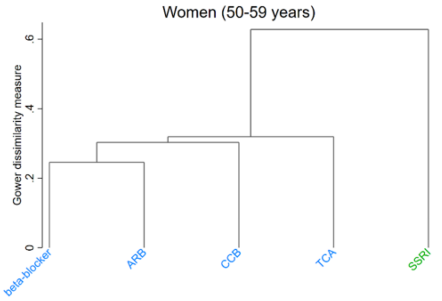
In women, the clusters became more similar to men. Two distinct clusters arised: a cardiovascular system cluster (beta-blocker, ACE-inhibitor and CCB); and SSRIs now start clustering with ARBs.

3.4 | ≥80 years

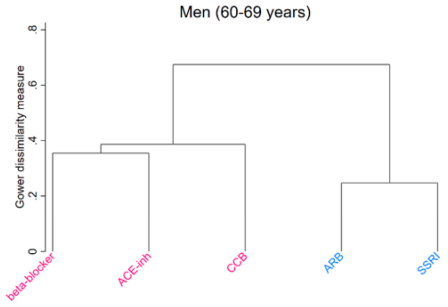
In the oldest group, the two distinct clusters identified in men aged 70–79 years remained the same. These were: cardiovascular system drugs (beta-blocker plus ACE-inhibitor); and antihypertensive plus



Men 50-59 years clusters
Cluster 1: beta-blocker, TCA, SSRI
Cluster 2: ACE-inhibitor, CCB

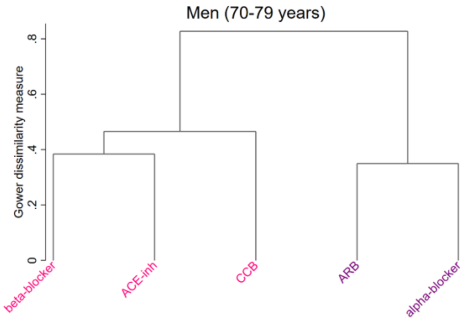


Women 50-59 years clusters
Cluster 1: beta-blocker, ARB, CCB, TCA

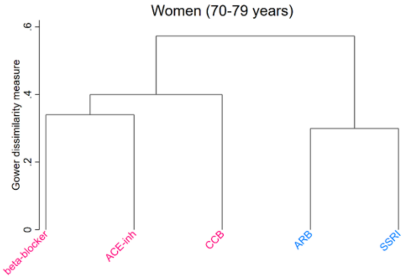


Men 60-69 years clusters
Cluster 1: beta-blocker, ACE-inhibitor, CCB
Cluster 2: ARB, SSRI

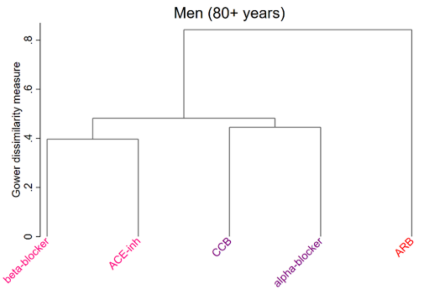
Women 60-69 years
Cluster 1: beta-blocker, ARB, TCA



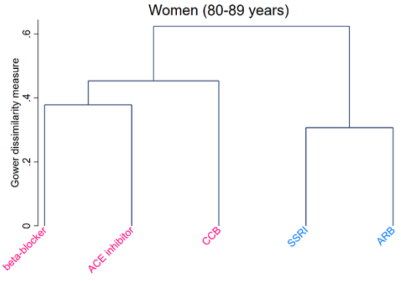
Men 70-79 years clusters
Cluster 1: beta-blocker, ACE-inhibitor- CCB
Cluster 2: ARB, uro-selective alpha-blocker



Women 70-79 years clusters
Cluster 1: beta-blocker, ACE-inhibitor, CCB
Cluster 2: ARB, SSRI



Men 80+ years clusters
Cluster 1: beta-blocker, ACE-inhibitor
Cluster 2: CCB, uro-selective alpha-blocker



Women 80+ years clusters
Cluster 1: beta-blocker, ACE-inhibitor, CCB
Cluster 2: SSRI, ARB

Note: drugs which are joined together lower in the diagram are more similar than those connected at a higher level

FIGURE 1 Cluster analysis dendrograms by sex and age-band. *ACE, angitotensin converting enzyme; ARB, angiotensin II receptor blocker; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SGLT2, sodium-glucose cotransporter-2.

uroselective alpha-blocker. The two clusters in women were identical to those aged 70–79.

3.5 | Overview

Overall, three main clusters emerged: combinations of cardiovascular system drugs (e.g. ACE-inhibitor and CCB were co-prescribed in 69 378 people (11.5%)); cardiovascular system plus psychoactive drugs (e.g., ARB and SSRI were co-prescribed in 10 017 people (1.6%)); and cardiovascular system plus uroselective alpha-blocker drugs in men (e.g., CCB and alpha-blocker were co-prescribed in 20 927 men (7.4% of men)).

4 | DISCUSSION

We identified distinct clusters of drugs commonly in use that are known to individually cause orthostatic hypotension, with the potential for additional synergistic harms when used in combination. Overall, clusters of different cardiovascular system drugs were notable in men and women of all ages. Cardiovascular system plus psychoactive drug clusters were common in women at all ages and men under 70 years. Cardiovascular system plus uro-selective alpha-blockers were significant in men ≥70 years. Many of these are common prescriptions in this older population.

This is the first study to describe medication clusters associated with orthostatic hypotension in older people in current practice. We report common, potentially harmful co-prescriptions that may be associated with cumulative risk of orthostatic hypotension. The main strength of this study is the large population sample (just over 600 000 older people) with complete prescription data enabling data-driven cluster analysis. IMRD is also broadly representative of patients in the UK primary care in terms of demographics.

There are, however, limitations in describing drug co-prescription patterns. Firstly, we only looked at drug groups associated with orthostatic hypotension identified in a recent systematic review of RCTs.[10] While this covers the main groups in the literature, there are some drug groups listed in other sources that were not examined, for example, benzodiazepines and opioids.[3] Prescription data in IMRD relates to medications prescribed by a GP, but do not necessarily reflect patient use and compliance. Our study does not include drugs that can be bought over the counter or drugs prescibed in secondary care (this is a very small proportion, but might include some anti-psychotic drug prescribing). Furthermore, our study reports on co-prescriptions over 1 year; therefore it is not known whether all the medications in clusters were taken simultaneously, as prescribing could have occurred anytime over this year. We limited our analysis to examining drugs by BNF sub-chapter, and therefore do not report more detailed data on combinations of individual drugs within classes. We used a high-level cluster analysis to identify common co-prescriptions of two and three drugs most relevant to clinical practice and practical for identifying potentially harmful drug combinations.

The results in this study are similar to a cluster analysis of primary care patients by Guisado-Clavero et al, focusing on older adults with multimorbidity and not on drugs potentially causing orthostatic hypotension. cardiovascular system and CNS drugs were among the most commonly prescribed.[11] They also identified a distinct medication pattern of cardiovascular system drugs plus antidepressants in women. The other medication patterns were linked to prevalent comorbidities, including a distinct cardiovascular system and CNS pattern, similar to our findings. Other drugs featured in the clusters included common musculo-skeletal and respiratory drugs (not included in this study as they are not known to be associated with orthostatic hypotension).[11]

We found that cardiovascular system clusters were common in all groups at all ages between 50 and ≥ 80, which is unsurprising since heart disease is a leading cause of death in older adults.[25] The distinct cardiovascular system cluster emerged later in women. This is consistent with the later development of cardiovascular disease (CVD) in women, compared with men.[25] In a study describing antihypertensive trends in CPRD, nearly a quarter of all adult primary care patients were prescribed an antihypertensive and overall patients were prescribed a median of 2 drug classes. Similar to our results, the prescription prevalence was highest for ACE inhibitors, CCBs and beta-blockers.[26]

Rouette et al. found beta-blockers were highly prevalent in the oldest patients (over 80 years).[26] We found that beta-blockers were prescribed in 23%–27% of older adults and present in every cluster in both sexes. This could be related to its broad indications: historic prescriptions of beta-blockers for hypertension (prior to 2010 when beta-blockers were no longer recommended as the first-line therapy for hypertension in the UK); rate control for arrhythmias and heart failure; migraine prophylaxis; and anxiety.[26] Although propranolol is licensed for anxiety symptom management, there is limited evidence of its safety in older adults.[26] Beta-blockers were found to be associated with a 7-fold increased risk of orthostatic hypotension compared with placebo in RCTs (likely related to their sympathetic inhibitory effects rather than effects on heart rate).[10] Therefore, its presence in clusters with other drugs associated with orthostatic hypotension is concerning, given the potential risk of a synergistic effect with drug–drug interactions.

We found cardiovascular system drugs plus antidepressants (TCAs and SSRIs) were a significant cluster in women of all ages and in men under 70 years. CVD and depression are prevalent in older people, and there is a bidirectional association between the two conditions.[27] In the previous study, treatment rates with antidepressants in older people with a new depression diagnosis was found to be high (87.1%), and increased both the youngest and the oldest age group (≥85 years).[28] TCAs, in particular, are known to be associated with a 6-fold increased risk of orthostatic hypotension compared to placebo and are used for many indications in older people, including insomnia and pain.[10] SSRIs have been strongly associated with falls.[29] Recent NICE guidance also warns that polypharmacy with antihypertensive and antidepressant medicines is often the cause of orthostatic hypotension in older people.[30]

Previous studies have found that women are more likely to be prescribed antidepressants than men.[31,32] Women are more likely to seek healthcare and obtain a depression diagnosis than men.[31] The diagnostic criteria for depression also originates from symptoms in women, which may under-detect depression in men who present differently.[31] This may explain why antidepressants were not identified in the clustering for men aged over 70 years. This could also be related to expected changes in the life course, as CVD becomes a more substantial burden in comparison to mental health conditions in older men.[25]

Our study identified a distinct cluster of cardiovascular system drugs plus uroselective alpha-blockers in older men above 70 years. Uro-selective alpha-blockers rarely feature as prevalent drugs in general studies looking at the medication patterns in older adults with multimorbidity.[11,33] They are, however, commonly prescribed in older men (18% of men aged over 50 years in our study) for symptoms of benign prostatic hyperplasia (BPH) and almost double the odds of orthostatic hypotension compared to placebo in RCTs.[10] They, therefore, may pose significant risk when prescribed in combination with other cardiovascular system drugs.

Our study has identified distinct clusters of drugs associated with orthostatic hypotension which change over the life course in men and women. The overall cumulative risk of orthostatic hypotension with drugs taken in combination will be influenced by the risk of the individual drugs, their mechanisms of action and dose.[10,34] Age also increases susceptibility to orthostatic hypotension through age-related physiological changes[4] and changes to the pharmacokinetics of a drug (e.g., how the drug is processed and excreted), increasing susceptibility to side effects.[3] Therefore the clusters identified in older people aged ≥70 may pose the greatest risk.

5 | CONCLUSION

Previous evidence has suggested that when single drugs associated with orthostatic hypotension are combined, there is a cumulative increased risk of orthostatic hypotension in older people.[2–8] In this study, we have identified that these combinations are commonly being prescribed together in practice. Future studies could investigate the potential for harm with such drug combinations and quantify this. Clinical guidelines for managing drug-induced orthostatic hypotension are either limited[35] or provide generic advice about eliminiating potentially causative drugs.[36] Whilst we acknowledge that many of these co-prescriptions may be clinically indicated where the benefits outweigh risks (e.g. combinations of antihypertensives for adequate blood pressure control), we suggest clinicians should be aware of the potential of synergistic harm with these combinations. Clincians should potentially monitor for orthostatic hypotension if using them—particularly as they commence new agents, in patients aged ≥70 or patients that are high-risk due to comorbidity. If monitoring for orthostatic hypotension is not feasible, then advising patients of the risk of orthostatic hypotension and symptoms to report, or home postural BP monitoring may be options. Our PPI group indicated that orthostatic hypotension symptoms (e.g., dizziness on standing) may not be recognized as important to report by older people. Future research should quantify the risk of orthostatic hypotension with these common drug combinations, and examine whether there are differences between individual drugs within classes.

ACKNOWLEDGMENTS

We would like to thank members of our patient and public advisory group, Maggie Kirby-Barr and Wesley Dowridge for their contributions to this study.

FUNDING INFORMATION

This work was funded by The Dunhill Medical Trust (DMT). CB is funded by a Research Training Fellowship from DMT (RTF1906\131).

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest in this work.

ETHICS STATEMENT

This study was approved by the Scientific Research Committee (SRC): SRC reference number: 20SRC055.

ORCID

Cini Bhanu https://orcid.org/0000-0002-3168-4172

REFERENCES

1. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011;21(2):69-72. doi:10.1007/s10286-011-0119-5
2. Gilani A, Juraschek SP, Belanger MJ, Vowles JE, Wannamethee SG. Postural hypotension. *BMJ*. 2021;373:n922. doi:10.1136/bmj.n922
3. Rivasi G, Rafanelli M, Mossello E, Brignole M, Ungar A. Drug-related orthostatic hypotension: beyond anti-hypertensive medications. *Drugs Aging*. 2020;37(10):725-738. doi:10.1007/s40266-020-00796-5
4. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(11):1294-1309.
5. Frith J, Parry SW. New horizons in orthostatic hypotension. *Age Ageing*. 2017;46(2):168-174. doi:10.1093/ageing/afw211
6. Wolters FJ, Mattace-Raso FUS, Koudstaal PJ, Hofman A, Ikram MA. Heart brain connection C. Orthostatic hypotension and the long-term risk of dementia: a population-based study. *Plos Med*. 2016;13(10). doi:10.1371/journal.pmed.1002143
7. Gibbon JR, Frith J. Orthostatic hypotension: a pragmatic guide to diagnosis and treatment. *Drug Ther Bull*. 2020;58(11):166-171. doi:10.1136/dtb.2020.000056
8. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. *J Clin Pharm Therapeut*. 2005;30(2):173-178. doi:10.1111/j.1365-2710.2005.00629.x[published
9. NICE Clinical Guidelines. *Blackouts*. National Institute for Health Research; 2021. Accessed October 12, 2022. https://cks.nice.org.uk/topics/blackouts.
10. Bhanu C, Nimmons D, Petersen I, et al. Drug-induced orthostatic hypotension: a systematic review and meta-analysis of randomised controlled trials. *PLoS Med*. 2021;18(11):e1003821. doi:10.1371/journal.pmed.1003821

11. Guisado-Clavero M, Violan C, Lopez-Jimenez T, et al. Medication patterns in older adults with multimorbidity: a cluster analysis of primary care patients. *BMC Fam Pract*. 2019;20(1):82. doi:10.1186/s12875-019-0969-9
12. IQVIA. Accessed October 12, 2022. https://www.iqvia.com/library/fact-sheets/uk-emr-iqvia-medical-research-data
13. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the health improvement network (THIN)database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*. 2011;19:251-255.
14. Vezyridis P, Timmons S. Evolution of primary care databases in UK: a scientometric analysis of research output. *BMJ Open*. 2016;6(10):e012785. doi:10.1136/bmjopen-2016-012785
15. Hobbs FDR, Bankhead C, Mukhtar T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007–14. *Lancet*. 2016;387(10035):2323-2330. doi:10.1016/s0140-6736(16)00620-6
16. Chisholm J. The read clinical classification. *BMJ*. 1990;300:1092.
17. NICE. Accessed October 12, 2022. https://bnf.nice.org.uk/
18. Zhang F, Mamtani R, Scott FI, Goldberg DS, Haynes K, Lewis JD. Increasing use of prescription drugs in the United Kingdom. *Pharmacoepidemiol Drug Saf*. 2016;25(6):628-636. doi:10.1002/pds.3947
19. Townsend P. Deprivation. *J Soc Policy*. 1987;16:125-146.
20. Horsfall L, Walters K, Petersen I. Identifying periods of acceptable computer usage in primary care research databases. *Pharmacoepidem Drug Saf*. 2013;22(1):64-69. doi:10.1002/pds.3368
21. Maguire A, Blak B, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidem Drug Saf*. 2009;18(1):76-83. doi:10.1002/pds.1688
22. Brian S, Everitt SL, Leese M, Stahl D. Cluster analysis. In: Balding NACC DJ, Garrett M, Fitzmaurice HG, et al., eds. *Wiley Series in Probability and Statistics*. 5th ed. John Wiley & Sons; 2011.
23. Gower JC. A general coefficient of similarity and some of its properties. *Biometrics*. 1971;827:857-871.
24. Bisquera A, Gulliford M, Dodhia H, et al. Identifying longitudinal clusters of multimorbidity in an urban setting: a population-based cross-sectional study. *Lancet Reg Health Eur*. 2021;3:100047. doi:10.1016/j.lanepe.2021.100047
25. Collaborators GBDA. Global, regional, and national burden of diseases and injuries for adults 70 years and older: systematic analysis for the global burden of disease 2019 study. *BMJ*. 2022;376:e068208. doi:10.1136/bmj-2021-068208
26. Rouette J, McDonald EG, Schuster T, Brophy JM, Azoulay L. Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study. *BMJ Open*. 2022;12(6):e057510. doi:10.1136/bmjopen-2021-057510
27. Zhang Y, Chen Y, Ma L. Depression and cardiovascular disease in elderly: current understanding. *J Clin Neurosci*. 2018;47:1-5. doi:10.1016/j.jocn.2017.09.022
28. Walters K, Falcaro M, Freemantle N, King M, Ben-Shlomo Y. Sociodemographic inequalities in the management of depression in adults aged 55 and over: an analysis of English primary care data. *Psychol Med*. 2018;48(9):1504-1513. doi:10.1017/S0033291717003014
29. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in people aged 20–64 years: cohort study using a primary care database. *BMC Med*. 2018;16(1):36. doi:10.1186/s12916-018-1022-x
30. NICE. Accessed November 22, 2022. https://cks.nice.org.uk/topics/blackouts/diagnosis/diagnosis/
31. Thunander Sundbom L, Bingefors K, Hedborg K, Isacson D. Are men under-treated and women over-treated with antidepressants? Findings from a cross-sectional survey in Sweden. *BJPsych Bull*. 2017;41(3):145-150. doi:10.1192/pb.bp.116.054270
32. Pal K, Sharma M, Mukadam NM, Petersen I. Initiation of antidepressant medication in people with type 2 diabetes living in the United Kingdom-a retrospective cohort study. *Pharmacoepidemiol Drug Saf*. 2022;31(8):892-900. doi:10.1002/pds.5484
33. Strampelli A, Cerreta F, Vucic K. Medication use among older people in Europe: implications for regulatory assessment and co-prescription of new medicines. *Br J Clin Pharmacol*. 2020;86(10):1912-1920. doi:10.1111/bcp.14462[published
34. Krum H, Conway EL, Broadbear JH, Howes LG, Louis WJ. Postural hypotension in elderly patients given carvedilol. *BMJ*. 1994;309(6957):775-776.
35. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people version 2. *Age Ageing*. 2015;44(2):213-218. doi:10.1093/ageing/afu145
36. NICE. Accessed November 22, 2022. https://cks.nice.org.uk/topics/blackouts/management/management/

How to cite this article: Bhanu C, Petersen I, Orlu M, et al. Drug-induced orthostatic hypotension: Cluster analysis of co-prescription patterns in older people in UK primary care. *Pharmacoepidemiol Drug Saf*. 2024;33(1):e5730. doi:10.1002/pds.5730