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SHORT REPORT

Characterising older adults’ risk of harm from blood-pressure lowering medications: a sub-analysis from the PRIME study

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Abstract

Aim: Cardiovascular disease (CVD) is common amongst frail older people. The evidence base for CVD commonly excludes older adults with multimorbidity or chronic conditions. Most cardiovascular drugs have the potential to lower blood pressure (BP) and therefore cause medication-related harm (MRH). We aimed to identify key clinical and sociodemographic characteristics associated with MRH in older people taking BP-lowering drugs for whatever indication they were prescribed.

Methods: The PRIME (prospective study to develop a model to stratify the risk of MRH in hospitalised elderly patients in the UK) study investigating the incidence and cost of MRH in older people across Southern England. Adults ≥65 years were recruited from five teaching hospitals at hospital discharge and followed up for 8 weeks. Telephone interviews with study participants, review of primary care records and hospital readmissions were undertaken to identify MRH. PRIME study participants taking BP-lowering drugs (as defined by National Institute for Health and Care Excellence hypertension guidelines) were included in this analysis.

Results: One hundred and four (12%) study patients experienced a total of 153 MRH events associated with BP-lowering drugs. Patients on four BP-lowering drugs were five times more likely to experience MRH compared to those taking one medication (OR 4.96; 95%CI 1.63–15.13; P = 0.01). Most MRH events were classified ‘serious’ (80%, n = 123), requiring dose change or treatment cessation. Almost half of MRH were potentially preventable (49%, n = 75).

Conclusion: Polypharmacy from BP-lowering drugs in older people is associated with preventable harm. Decisions around cardiovascular risk reduction should be carefully considered in view of MRH arising from BP-lowering drugs.

Keywords: medication-related harm, cardiovascular disease, hypertension, polypharmacy, frailty, older people

Key Points

• Cardiovascular medications with the potential to lower blood-pressure (BP) might cause harm to older adults. The characteristics of those most at risk have been scarcely explored.
• We found no association between sociodemographic characteristics of older adults and their risk of medication-related harm from BP-lowering drugs.
• Patients taking increasing numbers of BP-lowering drugs are at higher risk of medication-related harm in a dose–response relationship.
Background

Cardiovascular disease (CVD) including heart failure (HF), hypertension, and ischaemic heart disease (IHD) is common in multimorbid older adults [1]. Most cardiovascular guidelines and their evidence-base fail to include frail, older multimorbid adults [2]. The Hypertension in the Very Elderly Trial (HYVET) demonstrated that treatment of hypertension in patients over 80 was associated with a 23% reduced risk of CVD mortality [3]. However, HYVET participants had a median frailty index of 0.17 (IQR = 0.11–0.24), indicating that frail adults were under-represented in the study [4].

Cardio-active agents such as beta-blockers, calcium channel blockers and renin-angiotensin-aldosterone system antagonists act by lowering blood pressure (BP) to reduce cardiac workload. Meta-analysis of randomised trials show that the use of multiple BP-lowering drugs can be harmful, leading to treatment discontinuation from adverse reactions including hypotension and syncope [5, 6].

Decisions regarding CVD treatment benefit versus medication-related harm (MRH) risk in frail adults require an individualised, person-centred approach; this approach should be highlighted/evident in clinical practice guidance [7, 8].

Although the benefits of BP-lowering drugs have been well-researched, the extent and impact of harm caused have not. In the ‘Prospective study to develop a model to stratify the risk of medication related harm in hospitalized elderly patients in the UK’ (PRIME) patient cohort, BP-lowering drugs were the most prescribed medicines [9]. In this sub-analysis of PRIME, we will quantify serious MRH events such as death, hospitalisation and readmission from BP-lowering drugs [9, 10]. We explore clinical and sociodemographic characteristics predicting MRH in older people taking BP-lowering drugs which is key to optimising treatment decisions and reducing harm.

Methodology

Ethics approval for PRIME was granted by the National Research Ethics Service (REC reference 13/EE/0075).

Design, setting and participants

PRIME was a prospective cohort study that recruited patients aged ≥65, near the time of hospital discharge. The protocol and main results have been previously published [9, 10]. Patients were recruited from five NHS hospitals in the UK between September 2013 and November 2015. Participants were followed up for 8-week post-discharge to identify MRH incidence and cost.

In this sub-analysis, all patients receiving cardio-active drugs whose primary mode of action is by lowering BP were identified. Medication selection was based on National Institute for Health and Care Excellence (NICE) guidelines on hypertension management and WHO-ATC code [11, 12]. Patients prescribed angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers (ACEI/ARBs; WHO-ATC C09), calcium channel blockers (CCBs; WHO-ATC C08), thiazide or thiazide-like diuretics (WHO-ATC CO3A/CO3B), aldosterone antagonists (WHO-ATC CO3DA), beta-blockers (WHO-ATC C07) and other antihypertensives (WHO-ATC C02) were included in our analysis.

Outcomes

MRH was defined as harm from adverse drug reactions (ADR), harm from poor adherence and medication errors. This is a modified version of the definition by Strand et al. [13]. MRH incidence was determined by participant/carer interview at 8 weeks, using a structured questionnaire; review of GP records; and prospective review of hospital readmissions.

The Naranjo algorithm [14] was utilised to assess causality of MRH in conjunction with the British National Formulary and Summary of Product Characteristics. Medication adherence was assessed using a modified version of the Morisky scale [15].

MRH events were classified as ‘definite’, ‘probable’, ‘possible’, or ‘doubtful’ when no harm occurred [16–18]. Severity of MRH was graded using the approach of Morimoto et al. [19]: fatal, life-threatening, serious (needing dose change/treatment cessation), significant (MRH that did not meet the above criteria). Preventability of MRH was assessed using the Hallas et al. criteria [20]: ‘definitely preventable’ (treatment inconsistent with best practice or unrealistic), ‘possibly preventable’ (preventable with efforts exceeding obligatory clinical demands), ‘not preventable’, or ‘not able to evaluate’.

Statistical analysis

Baseline characteristics were compared between those who experienced MRH and those who did not experience MRH from BP-lowering medications. A chi-squared test of association was used for categorical data. The Mann–Whitney U test was used for non-normally distributed continuous data. Correlation was determined using Spearman’s rank-order coefficient.

Binary logistic regression was undertaken to assess the association between a range of clinical factors and MRH. Variables found to be statistically significant at $P < 0.05$ in univariate analysis were selected for inclusion in multivariate analysis. All selected variables were assessed for collinearity and association. Statistical analysis was performed using SPSS, version 26 (Armonk, NY, IBM Corp). As this is a hypothesis generating analysis, we did not adjust for multiple testing.
Table 1. Participant characteristics at baseline stratified by whether they experienced medication-related harm or not

| Characteristics                              | No medication-related harm (n = 737) | Medication-related harm (n = 104) | Total (n = 841) | P-value |
|----------------------------------------------|--------------------------------------|-----------------------------------|-----------------|---------|
| **Demographics**                             |                                      |                                   |                 |         |
| Age (years)                                  | 81 (75–86)                           | 83 (75–87)                        | 81 (75–86)      | 0.261a  |
| Gender (female) [%]                          | 429 (58)                             | 62 (60)                           | 491 (59)        | 0.7844  |
| Ethnic origin (White-British) [%]            | 708 (96)                             | 100 (96)                          | 808 (96)        | 0.8454  |
| Living alone [%]                             | 363 (50)                             | 57 (55)                           | 420 (50)        | 0.5604  |
| **Clinical and laboratory data**             |                                      |                                   |                 |         |
| Charlson Comorbidity Index [%]               | 2 (1–3)                              | 1 (1–3)                           | 2 (1–3)         | 0.149a  |
| Number of Charlson Comorbidity Conditions [%] |                                      |                                   |                 |         |
| 0–1                                          | 344 (47)                             | 56 (54)                           | 400 (48)        | 0.175c  |
| ≥2                                           | 393 (53)                             | 48 (46)                           | 441 (52)        | 0.286c  |
| Cognition (AMTS) [%]                         | 10 (9–10)                            | 9 (9–10)                          | 10 (9–10)       | 0.101c  |
| eGFR (ml/min)                                | 61 ± 22                              | 57 ± 18                           | 60 ± 22         | 0.859d  |
| Alcohol intake per week [%]                  | 444 (60)                             | 65 (63)                           | 509 (60)        | 0.859d  |
| 0–14 units [%]                               | 248 (34)                             | 34 (33)                           | 282 (34)        | 0.859d  |
| 15+ units [%]                                | 45 (6)                               | 5 (5)                             | 49 (6)          |         |
| **Medication detail**                        |                                      |                                   |                 |         |
| Number of antihypertensives [%]              | 2 (1–2)                              | 2 (1–3)d                          | 2 (1–2)         | <0.001d |
| Total number of regular medications [%]      | 10 (7–12)                            | 9 (7–12)                          | 10 (7–12)       | 0.100c  |
| Previous history of ADRs [%]                 | 242 (33)                             | 38 (37)                           | 280 (34)        | 0.494d  |
| Use of compliance aid [%]                    | 253 (34)                             | 37 (36)                           | 290 (35)        | 0.802d  |
| **Class of blood-pressure lowering medication** |                                      |                                   |                 |         |
| ACEI and ARBs [%]                            | 410 (56)                             | 68 (65)                           | 478 (57)        | 0.056c  |
| Beta-blockers [%]                            | 414 (56)                             | 56 (54)                           | 470 (56)        | 0.737c  |
| Calcium channel blockers [%]                 | 224 (30)                             | 50 (48)                           | 274 (33)        | 0.001c  |
| Aldosterone antagonists [%]                  | 76 (10)                              | 17 (16)                           | 93 (11)         | 0.066c  |
| Thiazide and thiazide-like diuretics [%]     | 59 (8)                               | 6 (6)                             | 65 (8)          | 0.424c  |
| Other antihypertensives [%]                  | 47 (6)                               | 12 (12)                           | 59 (7)          | 0.085c  |

*Median (IQR). **Mean ± SD. †Continuous data analysed using Mann–Whitney U test. ‡Categorical data analysed using Pearson’s χ². AMTS, abbreviated mental test score; ADR, adverse drug reaction; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers. *Drugs coded C02 (other antihypertensives); CO3A and CO3B (Thiazide and thiazide-like diuretics); C07 (Beta-blockers); C08 (Calcium Channel Blockers); C09 (ACEI/ARBs) on WHO-ATC system.

**Results**

**Participant characteristics**

Eight hundred and forty-one (66%) participants, median age 81 (IQR = 75–86) years, were prescribed BP-lowering drugs. Fifty-two percent (n = 441) had two or more co-morbidities. Fifty-three percent (n = 448) were on two or more BP-lowering drugs; 15% (n = 128) were on three or more drugs. The most prescribed drugs were ACEI/ARBs (57% of participants), beta-blockers (56% of participants) and CCBs (33% of participants; see Table 1).

**MRH incidence**

One hundred and four (12%) study participants experienced a total of 153 MRH events attributable to BP-lowering drugs. The main MRH events were dizziness (15%), peripheral oedema (14%), falls (13%) and postural hypotension (9%; Supplementary Table 1). ADRs accounted in 84% (n = 128) of MRH events. Non-adherence (4%; n = 6), medication errors (0%; n = 0) or a combination of ADRs, non-adherence and/or medications errors were less common (12%; n = 19; Supplementary Table 2).

ACEI/ARBs (33%; n = 50), CCBs (28%; n = 43) and beta-blockers (22%; n = 34) accounted for most MRH events. The frequencies of other classes of BP-lowering drugs leading to MRH including thiazide/thiazide-like diuretics, aldosterone antagonists and other antihypertensives, such as doxazosin and hydrazine were less frequent (Supplementary Table 1).

Of the 153 MRH events, 35% were definite (n = 54), 25% were probable (n = 38) and 40% were possible (n = 61). Eighty percent of the 153 MRH events were serious (n = 123), requiring dose change or treatment cessation (Supplementary Table 2).

Ten percent (n = 16) of the 153 MRH events were classified ‘definitely preventable;’ 39% (n = 59) were ‘possibly preventable’ and 22% (n = 34) were ‘not preventable’. We were not able to evaluate the MRH preventability in 29% of cases (n = 44).

**MRH risk factors**

Participants who experienced MRH were more likely to be on multiple BP-lowering drugs (OR 1.63; 95% CI 1.29–2.07). More specifically, participants prescribed a
Table 2. Variables associated with medication-related harm before and after adjusting for confounding factors in multivariate logistic regression analysis

| Variable                              | Unadjusted odds ratio (95% CI) | Adjusted odds ratio (95% CI) |
|---------------------------------------|--------------------------------|-----------------------------|
| Age (years)                           | 1.01 (0.99, 1.04)              | 1.02 (0.99, 1.05)           |
| Charlson Comorbidity Index            | 0.96 (0.86, 1.07)              | 0.96 (0.86, 1.08)           |
| Total number of blood-pressure lowering medications | 1.63 (1.29, 2.07)            | 1.45 (1.11, 1.88)           |
| CCB                                   | 2.03 (1.36, 3.03)              | 1.39 (0.86, 2.24)           |
| CCB and ACEI/ARB                      | 2.05 (1.09, 3.85)              | 1.37 (0.68, 2.76)           |
| CCB, ACEI/ARB and Beta-blocker        | 3.33 (1.41, 7.86)              | 1.40 (0.56, 3.75)           |

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval.

combination of CCBs, ACEI/ARBs and beta-blocker (OR 3.33; 95%CI 1.41–7.86) had the highest odds of experiencing MRH in univariate regression analysis. After adjusting for confounding factors including age and Charlson Comorbidity Index (CCI), only the total number of BP-lowering drugs a patient was taking was significantly associated with MRH (OR 1.45; 95%CI 1.11–1.88; Table 2).

There was a dose–response relationship between the number of BP-lowering drugs and proportion of patients experiencing MRH. Patients on four BP-lowering drugs were five times more likely to experience MRH compared to those only taking one drug (OR 4.96; 95%CI 1.63–15.13; Supplementary Figure 1). Age and CCI were not significantly associated with odds of experiencing MRH (Table 2). There was no correlation between CCI and the number of BP-lowering drugs ($r = -0.01; P = 0.84$).

Discussion

In this sub-analysis of the PRIME study, 12% of participants experienced MRH. Most events were serious, and 49% were potentially preventable. The likelihood of MRH increases with increasing number of BP-lowering medications; those on four BP-lowering drugs were five times more likely to suffer MRH compared to those on a single drug (OR 4.96; 95%CI 1.63–15.13; Supplementary Figure 1). These findings reinforce that a pro-active approach is warranted to reduce medication burden in frail older people.

Clinicians should adopt an individualised approach to balance the benefits of BP-lowering drugs versus their risk of MRH. Fifty-three percent of our study participants were on two or more BP-lowering drugs. Hypertension trials frequently report polypharmacy to achieve adequate BP control; in ‘The Systolic Blood Pressure Intervention Trial’ (SPRINT) 54% of participants required three or more medications [21], and in HYVET, 50% of participants required two drugs [3].

In a Cochrane meta-analysis, deprescribing antihypertensives had no impact on all-cause mortality or myocardial infarction. However, the low event rate and small studies made it difficult to make firm conclusions [22].

The current evidence from RCTs in CVD prevention/treatment in older people does not capture the heterogeneity of the older population and need for personalised treatment goals [2, 23]. Our PRIME study cohort is representative of frail older adults; 52% of participants had two or more co-morbidities. One limitation of our study was the fact that we could not elicit the exact indication for BP-lowering drugs use. Our cohort of older frail patients often had multiple indications for their BP-lowering drugs such as HF, hypertension and IHD, as is common in clinical practice. It is crucial to be vigilant when deprescribing in older adults with HF; Halliday et al. showed that 44% of participants developed worsening HF when medications were withdrawn [24]. A personalised approach is required as shown by Luymes et al., who showed that in patients with a low predicted CVD risk, deprescribing is safe in the short term but does not necessarily improve quality of life or reduce healthcare cost [25]. Taking patient preferences into consideration, deprescribing medications can be considered.

Conclusion

Polypharmacy from BP-lowering drugs in frail older people is associated with serious and potentially preventable harm. Decisions around cardiovascular risk reduction must be carefully considered using an individualised approach in view of the possibility of MRH arising from BP-lowering medications.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

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References

1. Marinus N, Vigorito C, Giallauria F et al. Frailty is highly prevalent in specific cardiovascular diseases and females, but significantly worsens prognosis in all affected patients: a systematic review. Ageing Res Rev 2021; 66: 101233. https://doi.org/10.1016/j.arr.2020.101233.

2. Krishnaswami A, Steinman MA, Goyal P et al. Deprescribing in older adults with cardiovascular disease. J Am Coll Cardiol 2019; 73: 2584–95.

3. Beckett NS, Peters R, Fletcher AE et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358: 1887–98.

4. Warwick J, Falaschetti E, Rockwood K et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYPertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo. BMC Med 2015; 13: 78. https://doi.org/10.1186/s12916-015-0328-1.

5. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens 2016; 34: 1921–32.

6. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment on cardiovascular outcomes and mortality: 13-benefits and adverse events in older and younger patients with hypertension: overview, meta-analyses and meta-regression analyses of randomized trials. J Hypertens 2018; 36: 1622–36.

7. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. Am Fam Physician 2013; 87: 331–6.

8. Parekh N, Page A, Ali K, Davies K, Rajkumar C. A practical approach to the pharmacological management of hypertension in older people. Ther Adv Drug Safety 2017; 8: 117–32.

9. Parekh N, Ali K, Stevenson JM et al. Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. Br J Clin Pharmacol 2018; 84: 1789–97.

10. Stevenson J, Parekh N, Ali K et al. Protocol for a prospective (P) study to develop a model to stratify the risk (R) of medication (M) related harm in hospitalized elderly (E) patients in the UK (the PRIME study). BMC Geriatr 2016; 16: 22. https://doi.org/10.1186/s12877-016-0191-8.

11. National Institute for Clinical Excellence. Hypertension in Adults: Diagnosis and Management. London, UK: NICE 2019 [Online]. https://www.nice.org.uk/guidance/ng136.

12. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - ATC/DDD Oslo, Norway: World Health Organisation, 2021 Index [Online]. https://www.whocc.no/atc_ddd_index/.

13. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. DICP, Ann Pharmacother 1990; 24: 1093–7.

14. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239–45.

15. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986; 24: 67–74.

16. Hanlon JT, Peiper CF, Hajjar ER et al. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. J Gerontol Ser A Biol Sci Med Sci 2006; 61: 511–5.

17. Hakkakainen KM, Gyllensten H, Jönsson AK, Andersson Sundell K, Petzold M, Hägg S. Prevalence, nature and potential preventability of adverse drug events - a population-based medical record study of 4970 adults. Br J Clin Pharmacol 2014; 78: 170–83.

18. Tångisuran B, Graham Davies J, Wright JE, Rajkumar C. Adverse drug reactions in a population of hospitalized very elderly patients. Drugs Aging 2012; 29: 669–79.

19. Morimoto T, Gandhi T, Seger A, Hsieh T, Bates D. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004; 13: 306–14.

20. Hallas J, Harvald B, Gram LF et al. Drug-related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med 1990; 228: 83–90.

21. Williamson JD, Supiano MA, Applegate WB et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years in a randomized clinical trial. JAMA - J Am Med Assoc 2016; 315: 2673–82.

22. Reeve E, Jordan V, Thompson W et al. Withdrawal of antihypertensive drugs in older people. Cochrane Database Syst Rev 2020; 6: CD012572.
23. Scott IA, Hilmer SN, Le Couteur DG. Going beyond the guidelines in individualising the use of antihypertensive drugs in older patients. Drugs Aging 2019; 36: 675–85.

24. Halliday BP, Wassall R, Lota AS et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet (London, England) 2019; 393: 61–73.

25. Luymes CH, Poortvliet RKE, van Geloven N et al. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster randomised non-inferiority trial. BMC Med 2018; 16: 5. https://doi.org/10.1186/s12916-017-0988-0.

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