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The association between gaps in antihypertensive medication adherence and injurious falls in older community-dwelling adults

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Injurious falls, older adults, antihypertensive medication, medication adherence, gaps in adherence

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Abstract

Objective

Growing evidence suggests that older adults are at an increased risk of injurious falls when initiating antihypertensive medication, while the evidence regarding long-term use of antihypertensive medication and the risk of falling is mixed. However, long-term users who stop and start these medications may have similar risk of falling to initial users of antihypertensive medication. Our aim was to evaluate the association between gaps in antihypertensive medication adherence and injurious falls in older (>65yrs) community-dwelling, long-term (>1yr) antihypertensive users.

Design

Prospective cohort study

Setting

Irish Community Pharmacy

Participants

Consecutive participants presenting a prescription for antihypertensive medication to 106 community pharmacies nationwide, community dwelling, over 65 years, with no evidence of cognitive impairment, taking antihypertensive medication for 1 year or longer (n=938).

Measures

Gaps in antihypertensive medication adherence were evaluated from linked dispensing records as the number of 5-day gaps between sequential supplies over the 12-month period prior to baseline. Injurious falls during follow-up were recorded via questionnaire during structured telephone interviews at 12-months.

Results

At 12-months, 8.1% (n=76) of participants reported an injurious fall requiring medical attention. The mean number of 5-day gaps in medication-refill behaviour was 1.47 *(1.58)*. In adjusted modified Poisson models 5-day medication-refill gaps at baseline was associated with a higher risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, *p*=0.024).

Conclusion

Each 5-day gap in antihypertensive adherence increased the risk of injurious falls by 18%. Gaps in antihypertensive adherence may be a marker for increased injurious falls-risk. It is unknown whether adherence-interventions will reduce subsequent risk. This finding is hypothesis generating and should be replicated in similar populations.

Strengths and limitations of this study

- Prospective cohort study of a community-dwelling older recruited from community pharmacies across the Republic of Ireland.
- Objective evaluation of medication exposures and medication adherence although injurious falls was self-reported which may lead to misclassification.
- Negative control exposure analyses to account for a potential healthy-adherer effect were conducted.
- Data on some important confounders, such as such as history of previous falls, frailty and disability, and the date of falls were not available to us.

Introduction

While many studies have demonstrated the benefits of antihypertensive agents on myocardial infarction and stroke risk reduction (1-3), concerns have been raised regarding the risk of falls associated with antihypertensive medications among older adults (4, 5). Growing evidence suggests that the associated risk of injurious falls varies according to the duration of treatment (5, 6). Studies have consistently shown that older adults are at a greater risk for injurious falls or hip fractures shortly after initiating antihypertensive medications (7-12). Although the underlying mechanism is unknown, it is thought that antihypertensive medication cause or exacerbate orthostatic hypotension in the elderly resulting in poor balance, weakness, dizziness and falls (5, 13-15). The prevalence of orthostatic hypotension increases with age and uncontrolled hypertension (16), and orthostatic hypotension itself is associated with an increased risk of injurious falls (17, 18). There is also evidence that initial antihypertensive medication use is associated with orthostatic hypotension as a result of reduced cardiac output and plasma volume (19, 20).

Observational studies investigating the risk of injurious falls among long-term users of antihypertensive agents have yielded mixed results (21-28). Despite the known risks associated with treatment initiation, studies of long-term users have not considered the potential effect of medication adherence, specifically the quality of daily dose-taking behaviour of patients, known as dose-implementation (29), on risk of injurious falls. It is plausible that failure to consistently take antihypertensive medications may result in fluctuations in blood pressure, which could lead to an increased risk of falls (30). A study of electronically compiled dosing histories revealed intervals between antihypertensive doses to be prevalent. On any given day 10% of doses were omitted, with 43% of missed doses occurring during a sequence of three or more days of missed doses. Overall approximately half of patients omit doses for ≥ 3 days at least once a year (31). The quality of implementation of a medication regimen should be interpreted according to the pharmacology of the drug. During gaps in antihypertensive medication use, the pharmacological effects

on blood pressure will gradually diminish (32-34), and upon resumption of therapy patients may experience acute changes to blood pressure similar to initial use.

Our aim was to evaluate the quality of dose-implementation with long-term (>1 year) antihypertensive medication use and evaluate its association with injurious falls in a cohort of community-dwelling older adults (>65 years).

Methods

Study Setting and Design

We conducted a prospective cohort study, recruiting participants from 106 community pharmacies across the Republic of Ireland between March and May 2014. Pharmacies were selected on the basis of participating in the National Pharmacy Internship Programme. Participants completed a structured telephone interview with trained pharmacy interns at baseline and 12 months. Interviews were subsequently linked to each patients' pharmacy records. We evaluated the quality of dose-implementation using pharmacy records for the 12-months prior to baseline, with 5-day gaps in prescription-refill flagged as poor dose-implementation. Injurious falls were assessed via self-report at 12-month interview. Participants provided written informed consent. Ethical approval for this study was granted by the Research Ethics Committee of the Royal College of Surgeons in Ireland.

Patient involvement

No patients were involved in this study.

Inclusion/exclusion criteria

Each pharmacy recruited 15 consecutive participants presenting with a prescription for at least one medication for hypertension, aged >65 years, community-dwelling, able to speak and understand English with no evidence of cognitive impairment as judged by the pharmacist. Patients dispensed anticholinesterase medication or memantine during the study period, a proxy indicator of cognitive impairment, were excluded due to poor recall of falls and associations with lower medication adherence. We excluded participants reporting use of antihypertensive medication for less than 12 months and participants attending other pharmacies as their pharmacy records were not complete.

Outcome

Injurious falls were assessed during the 12-month follow-up period (April 2014 - May 2015). At 12-month follow-up interview we asked participants, “Have you fallen in the last year?” and “Did you injure yourself seriously enough to need medical treatment”. A standard definition of a fall as “an unexpected event in which participants come to rest on the ground, floor, or lower level” was used (35). Injurious falls are likely to be recalled more accurately due to the subsequent medical treatment (36).

Exposure

We evaluated quality of dose-implementation for the 12-month period prior to baseline (March 2013 - April 2014), by measuring the number of 5-day gaps in prescription refill from linked patient pharmacy records. Pharmacy dispensing records are an objective and indirect measure of medication adherence (37-39). We chose a 5-day gap based on literature describing the gradual decline of antihypertensive medication effect on blood pressure over three days (32-34), extending this period to five days due to the indirect method of adherence measurement, and to allow for potential variation in antihypertensive medication pharmacology (40). The number of occasions that gaps of five days occurred between sequential supplies during the previous 12 months was evaluated at baseline. Oversupplies were credited to a maximum excess of 180 days of medication.

Covariates

Confounding factors were chosen based on known associations with falls and medication adherence behaviour. Age, gender, marital status, education level and comorbidities including depression, diabetes mellitus, rheumatoid arthritis and stroke were recorded at baseline interview (41). Parkinson’s disease and urinary incontinence were identified by proxy from medication (ATC N04; ATC G04BD) (41). A meta-analysis by Woolcott et al was used to classify medication as falls-risk increasing drugs (antipsychotics, antidepressants, benzodiazepines, NSAIDs, opiates, and sedatives) from linked dispensing records (42).

The number of regular medicines dispensed may also be associated with an increased falls risk (27, 43). Class of antihypertensive used may affect falls risk, for example, ACEIs and ARBs have been observed to lower the risk of falls (21, 24). Moderate (22) and high (25) doses have also been linked to an increased falls risk. Standardised doses of antihypertensive medication were determined using the World Health Organisation's Daily Defined Dose (WHO-DDD). Addition and titration of antihypertensive medication may precipitate a fall (11) and a binary variable was created to account for this during follow-up.

Statistical analysis

Descriptive statistics are presented for participant characteristics at both baseline and follow-up. Means and standard deviations are presented for continuous variables; counts and proportions for categorical variables. The association between 5-day gaps in medication-refill and injurious falls during follow-up was estimated using modified Poisson regression to obtain relative risks rather than odds ratios, which is considered more suitable when outcomes are not rare (44). Standard errors were adjusted in regression models using the Sandwich-estimator, due to potential for dependency of observations at the pharmacy-level. The final multivariable model was adjusted for all covariates.

Sensitivity analysis

Due to concerns of multivariable regression models with many confounders and low number of outcome events we also undertook a sensitivity analysis using a propensity score covariate adjustment model. To reduce the number of confounders we estimated a Poisson model with 5-day gaps in antihypertensive prescription refills as outcome and all other covariates as predictors. The predicted value from the resultant regression equation for each observation was then used to adjust for covariates in the final modified Poisson regression model with injurious falls as outcome and number of 5-day gaps in antihypertensive prescription refill as the predictor variable (45).

Negative control analysis

Finally, a negative control exposure model was also estimated. Negative controls are a tool for detecting confounding bias in observational studies (46). To detect suspected confounding resulting from the healthy-adherer bias, whereby patients with poorer medication adherence tend to have worse outcomes (47), the association between 5-day gaps in medication taking behaviour to anti-thrombotic medication and injurious falls was also estimated. Anti-thrombotics (ATC Code B01AC, B01AE, B01AF e.g. aspirin, dabigatran, rivaroxaban) were chosen due to high prevalence of use in this sample and the lack of a theoretical association with falls. An association between gaps in anti-thrombotic medication adherence and injurious falls would indicate the presence of confounding associated with the exposure variable (48). The characteristics of the subsample may differ statistically from the entire sample (n=938) and introduce bias into the estimates of the negative control analysis. Differences in participant characteristics between those using anti-thrombotic and those not using anti-thrombotic medication was thus also evaluated using Pearsons' $\chi 2$ and *t*-tests. Based on these differences an additional weighted negative control regression analysis using inverse probability weights was undertaken. Weights were estimated as the ratio of the predicted probabilities using two probit regressions, one with and one without statistically different participant characteristic variables.

Statistical modelling was performed using Stata version 14 (StataCorp College Station, Texas, USA).

Results

Nine hundred and thirty-eight participants met the inclusion criteria. The mean age of this sample was 76.1 years and 47.9% were men. The mean duration of antihypertensive therapy was 11.7 years with participants taking a mean of 2.1 different classes of antihypertensive medication. Participants reported a mean of 2.4 additional co-morbid conditions and were taking on average 6.2 regular medication. Table 1 provides a summary of participant characteristics at baseline and 12-month follow-up.

During 12-months follow-up, 8.1% (n=76) of participants reported an injurious fall requiring medical attention or treatment. At baseline the mean number of 5-day gaps in medication-refill behaviour was 1.47 *(sd 1.58)*.

Primary analysis

Table 2 details the results of the modified Poisson regression model. In the adjusted analysis, 5-day medication-refill gaps at baseline was prospectively associated with a higher risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). As demonstrated in Figure 1, each 5-day gap in antihypertensive medication adherence was associated with an 18% increased risk of an injurious fall during follow-up.

Sensitivity analyses

Table 3 presents the results of our sensitivity analyses. The propensity score covariate adjustment model produced similar estimates (aRR 1.17, 95% CI 1.03 – 1.35, p=0.020) to our primary analysis.

Negative control analysis

For the negative control exposure analysis, 60% (n=566) of participants were regularly using anti-thrombotic medication. The mean number of 5-day gaps in anti-thrombotic prescription refill was 1.28 (*1.40)*. Table 4 presents the results of the negative control analysis. In multivariate modified Poisson regression analysis, adjusted for covariates, 5-day gaps in anti-thrombotic medication-refill behaviour

was not associated with injurious falls (aRR 1.04, 95% CI 0.84 – 1.28, *p*=0.728). In comparison to the antihypertensive sample (n=938), the anti-thromobotic sample consisted of a statistically significant higher proportion of males, a higher rate of co-morbidities and higher rate of regular medication use. To adjust for potential bias, this subsample of 566 participants was re-weighted using inverse probability weights, estimated as the ratio of the predicted probabilities using two probit regressions, one with and one without statistically significant variables (gender, co-moribidites, regular medication use). In weighted multivariate modified Poisson regression analysis similar estimates were observed. Adjusting for covariates, 5-day gaps in anti-thrombotic medication-refill behaviour was not associated with injurious falls (aRR 1.04, 95% CI 0.85 – 1.29, *p*=0.672).

Participant attrition

Participants excluded due to attending other pharmacies, tended to be younger, were less likely to report a heart-attack and reported fewer co-morbidities, however there was no differences in injurious falls reported or number of medication gaps between those included and excluded from the analysis.

Missing data

In the complete case multivariate analysis (n=724) for the association between 5 day gaps in antihypertensive adherence and injurious, 22.8% of observations were dropped due to missing data. The largest source of missing data was due to the variable indicating addition/titration of antihypertensive medication during follow-up (n=156). This missing data was attributed to incomplete extraction of dispensing records at 12-month follow-up. Removing this variable from the final multivariate model yielded a model with a higher number of observations (n=856) and similar estimates for the association between 5 day gaps in adherence and injurious falls (aRR 1.16, 95% CI 1.02-1.31, *p*=0.019). Multiple imputation was also undertaken utilising a multivariate normal distribution, Markov Chain Monte Carlo

procedure and 100 imputations. In this multiple imputation similar estimates were obtained (aRR 1.15, 95% CI 1.02-1.30, *p*=0.020).

Discussion

Principal findings

We observed an 18% increased risk of an injurious fall for each 5-day gap in antihypertensive medication adherence. This finding was statistically significant following adjustment for a large number of clinically relevant fall risk factors including age, gender, co-morbidities and fall-risk increasing medication. Furthermore, a negative control exposure model did not indicate the potential for confounding due to the healthy-adherer bias.

Findings in the context of previous literature

This is the first study to examine the quality of dose-implementation on the risk of falls associated with antihypertensive medication use. A previous study by Berry et al identified an increased risk of falls for patients reporting lower medication adherence. They used a subjective method to evaluate medication adherence and did not differentiate adherence between drug classes (30). In contrast, we used an objective method to evaluate the quality of dose-implementation and applied it to the exposure of interest, identifying that almost two-thirds of community-dwelling adults had at least one gap in antihypertensive medication-refill over 12-months. A number of observational studies have consistently identified a higher risk of falling following antihypertensive medication initiation or titration (7-12). It has been suggested that the underlying mechanism is antihypertensive medication induced acute orthostatic hypotension (5). Orthostatic hypotension is associated with an increased risk of injurious falls (17, 18). Patients with poor implementation of antihypertensive pharmacotherapy, characterised by gaps in antihypertensive medication use, may experience a gradual rise in blood pressure (32-34). Upon resumption of therapy, acute orthostatic hypotension, similar to initial use, may occur, placing patients at a greater risk for falls relative to those who do not have gaps in antihypertensive therapy. Further research is needed to investigate such a mechanism. Regardless, consistent evidence indicates initiating, titrating and adding antihypertensive medication is associated with a short-term increased risk of

injurious falls (7-12). Patients with gaps in their adherence to these therapies will potentially be exposed to similar pharmacological effects experienced on initiating antihypertensive medication.

There are conflicting findings on the association between falls and long-term antihypertensive use. Higher doses of antihypertensive medication (22, 25), and the use of loop diuretics (23) and non-selective beta-blockers (26, 28) have been linked to falls, whereas a protective effect for the use of ACEIs and ARBs has been reported (24). Furthermore two recent studies have found no association between antihypertensive medication use and falls in older adults (21, 27). A limitation to these studies is the failure to evaluate patients' medication adherence, potentially confounding findings. Chronic use of antihypertensive medication may improve systemic and cerebral haemodynamics, and reduce orthostatic hypotension, leading to a reduction in injurious falls (17, 21). However failing to account for medication adherence in long-term users may confound the association between antihypertensive use and injurious falls. Furthermore, medication adherence is known to vary according to class of antihypertensive medication, with higher adherence associated with ACE inhibitors and ARBs, and lower adherence associated with diuretics and beta-blockers (49). These associations may be an explanatory factor for the protective effect observed for ACE inhibitors and ARBs, and the adverse effect observed for diuretics and beta-blocker on falls risk. Findings from randomized controlled trials of antihypertensive medication have reported no increase in falls risk (3, 50-52). Nonetheless, trials tend to be of healthier populations that are not readily generalizable to real world settings (53, 54). For example the recent SPRINT trial demonstrated in adults older than 75 years, that intensive blood pressure control was not associated with an increase in injurious falls (52). However the external validity of this finding is questionable. A nationally representative longitudinal study of older adults meeting the SPRINT inclusion criteria observed a 5-fold higher rate of injurious falls than the standard care group within SPRINT during a comparable follow-up period (55). Furthermore, it is apparent that medication adherence of clinical trial participants is higher. Two-thirds of our real-world participants had at least one 5-day gap in

antihypertensive medication-refill over a 12-month period compared to only half of clinical trial participants who miss three consecutive days of antihypertensive within the same time period (31).

Strengths and limitations

A strength of this study was the recruitment of community-dwelling older people from a national sample of pharmacies in Ireland, although the non-probabilistic consecutive recruitment method may introduce selection bias. These findings are likely to be only generalisable to those taking antihypertensive medication for longer than 1 year, and who consistently attend the same pharmacy to obtain antihypertensive medication. Participants that we excluded because of attending other pharmacies were more likely to be younger and report less co-morbidities. Additional strengths of this study include the prospective evaluation between medication-gaps (measured prior to baseline) and injurious falls (evaluated from baseline to end of follow-up), with covariates remaining relatively consistent between baseline and follow-up. However, it was not possible to fully observe the temporal association between exposure and outcome, as the date of falls was not available. There are also limitations to the use of a self-report measure of injurious falls. Injurious falls recalled over a 1 year period however, are recalled more accurately than other fall outcomes (36). Furthermore we observed comparable rates of injurious falls to similar studies of older adults in Ireland and the UK (18, 56). Excluding participants with possible cognitive impairment and dementia may have minimized fall recall misclassification. However our methods to evaluate cognitive impairment may have resulted in misclassification due to potential under-diagnosis of patients in community settings (57). We also used an indirect method to evaluate medication adherence. Dispensing of medication from the pharmacy does not necessarily prove consumption (37). However, by evaluating medication-refill adherence using a gap method, we can identify definitive periods where participants had at least 5-days during which they had insufficient medication to continuously consume antihypertensive medication until obtaining a

subsequent supply. The resultant misclassification of medication adherence would weaken associations between medication-refill gaps and injurious falls.

Additional strengths include the adjustment for a large number of potential confounders, including demographics, medical history and medication use. Furthermore, in comparison to other observational studies, medication use was evaluated objectively using pharmacy records, and concurrent changes to antihypertensive therapy including addition of classes and titration of doses were controlled. Only established fall-risk increasing drugs were considered, hence only specific drugs or classes identified in previous meta-analysis were included (42). Due to potential issues of testing a large number of predictors on a binary outcome with a low number of events in multivariate regression, a propensity score covariate adjustment model was also estimated, which did not change findings (45). The possibility for residual confounding may remain. Participants' blood pressure during the follow-up period was not measured to assess fluctuations in blood pressure. However the ability of antihypertensive drugs to lower blood pressure have been proven in clinical trials (1-3), and clinical studies have shown that withdrawal of these medications leads to a gradual rebound in blood pressure (32-34). Furthermore, the feasibility of undertaking these measurements, which would likely require daily measurements, is unlikely in large observational studies such as this. Indeed measuring patient blood pressure on a daily basis would change the medication-taking behaviour of participants, known as white-coat adherence (58, 59), which is similar to the Hawthorne effect. Some important fall-risk factors were also unmeasured such as history of previous falls, frailty and disability (41). However, a negative control exposure analysis was undertaken to evaluate the potential for residual confounding. In the negative control model no association between gaps in anti-thrombotic medication adherence and injurious falls was observed. Theoretically there should be no association and the negative control exposure model indicates potential confounding resulting from the healthy adherer bias is unlikely (46, 47).

Conclusion

An 18% increased risk of an injurious fall associated with each 5-day gap in antihypertensive medication adherence was observed. Our findings should be considered as hypothesis generating and future research should attempt to fully test the temporal relationship with injurious falls. If feasible, a direct method, such as electronic dose monitoring devices, should be used to evaluate quality of dose-implementation. Clinicians reconciling the risk of falls in older patients prescribed antihypertensive medication, could use gaps in antihypertensive medication adherence as a marker to identify patient at higher risk of injurious falls. Although further research is needed to investigate whether improving adherence to antihypertensive medication can reduce injurious falls, advising patients to consistently take antihypertensive medication will reduce cardiovascular disease risk.

Author Statement

PD, SS, PG, GC were involved in the conception and design of the study. PD and GC undertook the acquisition, and analysis of the work. PD, SS, PG, GC interpreted the data. PD, SS, PG, GC drafted the manuscript. PD, SS, PG, GC revised the manuscript and gave final approval of the version to be published. PD, SS, PG, GC agree agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflicts of Interest: None to declare

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Data sharing statement No additional data available.

Tables

Table 1 A summary of participant characteristics as evaluated at baseline interview and follow-up via questionnaire and via linked dispensing records (n=938)

	Baseline	Follow-up
Demographics		
Age, *mean* (SD)	76.1 (*6.1*)	77.1 (*6.1*)
Male, % (*n*)	47.9 (449)	47.9 (449)
Year on AHT meds, *mean* (SD)	11.7 (*8.9*)	12.7 (*8.9*)
Education		
Primary, % (*n*)	26.7 (250)	26.7 (250)
Secondary, % (*n*)	42.0 (394)	42.0 (394)
Third-Level, % (*n*)	26.4 (248)	26.4 (248)
Marital Status		
Married/Partner, % (*n*)	59.3 (556)	58.4 (548)
Single/Divorced/Widow, % (*n*)	37.4 (351)	39.1 (367)
Medical History		
Depression, % (*n*)	13.3 (125)	13.9 (131)
Stroke, % (*n*)	3.5 (33)	3.5 (33)
Arthritis, % (*n*)	43.7 (410)	48.1 (451)
Diabetes, % (*n*)	20.5 (192)	21.5 (202)
Morbidity Count, *mean* (SD)	2.4 (*1.6*)	2.5 (*1.7*)
Medication History		
Alpha-blocker, % (*n*)	6.7 (63)	5.2 (49)
Beta-blocker, % (*n*)	48.4 (454)	42.4 (398)
Diuretic, % (*n*)	29.6 (278)	23.8 (223)
Calcium antagonists, % (*n*)	43.9 (412)	37.5 (352)
Angiotensin inhibitors/blockers, % (*n*)	77.6 (728)	64.1 (601)
Number of AHT classes, *mean* (SD)	2.1 (*1.0*)	2.1 *(0.9*)
AHT WHO-DDD, *mean* (SD)	2.7 (*2.2*)	2.6 (*1.9*)
Antipsychotics, % (*n*)	2.8 (26)	2.0 (19)
Antidepressants, % (*n*)	15.6 (146)	13.5 (127)
Benzodiazepines, % (*n*)	9.2 (86)	7.2 (68)
NSAIDs, % (*n*)	9.1 (85)	6.0 (56)
Opiates, % (*n*)	6.2 (58)	5.7 (53)
Parkinson's disease, % (*n*)	1.1 (10)	1.3 (12)
Sedatives, % (*n*)	8.2 (77)	8.5 (80)
Urinary Incontinence, % (*n*)	5.4 (51)	5.4 (51)
Number of regular medicines, *mean* (SD)	6.2 (*3.7*)	5.9 (*4.1*)

% may not add up to 100% due to missing data. AHT=antihypertensive medication.

Table 2 The estimates, 95% confidence intervals and *p*-values for the association between 5-day gaps in antihypertensive medication adherence and injurious falls

	Crude RR	95% CI	*p*	Adj. RR	95% CI	*p*
Medication-Refill Gaps ≥5 days	1.14	1.02 - 1.28	0.023	1.18	1.02 - 1.37	0.024
Age	1.06	1.02 - 1.10	0.004	1.06	1.01- 1.12	0.029
Female gender	2.12	1.28 - 3.50	0.004	2.00	0.95 - 4.20	0.067
***Education* Primary**	Ref	-	-	-	-	-
Secondary	1.61	0.90 - 2.87	0.109	2.00	1.04 - 3.85	0.038
Third-level	1.41	0.70 - 2.83	0.331	1.54	0.66 - 3.55	0.315
***Marital Status* Married/Partner**	Ref	-	-	-	-	-
Single/Widow/Div	1.34	0.87 - 2.06	0.183	0.85	0.49 - 1.48	0.566
Depression	0.87	0.39 - 1.94	0.737	0.25	0.08 - 0.84	0.025
Stroke	0.74	0.19 - 2.90	0.666	1.01	0.18 - 5.67	0.990
Arthritis	1.51	0.95 - 2.37	0.078	0.80	0.47 - 1.38	0.426
Diabetes	0.73	0.39 - 1.35	0.312	0.71	0.35 - 1.44	0.346
Co-morbidity count	1.16	1.03 - 1.32	0.016	1.18	0.94 - 1.49	0.161
Alpha-Blocker	1.18	0.56 - 2.50	0.661	0.60	0.19 - 1.88	0.377
Beta-blocker	1.17	0.77 - 1.77	0.461	1.29	0.76 - 2.19	0.346
Diuretics	0.90	0.55 - 1.46	0.665	1.03	0.56 - 1.89	0.920
Calcium antagonists	1.02	0.68 - 1.54	0.918	1.14	0.65 - 1.98	0.653
Angiotensin inhibitors/blockers	0.73	0.45 - 1.19	0.212	0.84	0.46 - 1.54	0.576
Time since initial AHT Rx	1.01	0.99 - 1.03	0.465	1.01	0.99 - 1.03	0.400
Antihypertensive WHO-DDD	0.97	0.89 - 1.06	0.487	1.00	0.86 - 1.16	0.997
Addition/titration of AHT	1.67	0.97 - 2.90	0.064	1.87	0.99 - 3.55	0.054
Antipsychotics	0.94	0.23 - 3.80	0.933	1.52	0.34 - 6.75	0.581
Antidepressants	1.55	0.92 - 2.63	0.102	1.80	0.87 - 3.74	0.113
Benzodiazepines	2.03	1.20 - 3.44	0.008	1.29	0.62 - 2.68	0.493
NSAIDs	0.55	0.22 - 1.39	0.208	0.52	0.19 - 1.44	0.207
Opiates	2.28	1.27 - 4.09	0.006	2.00	1.06 - 3.76	0.032
Parkinsonian Drugs	2.49	0.70 - 8.85	0.158	2.97	0.44 - 20.0	0.263
Hypnotics and Sedatives	1.31	0.69 - 2.46	0.408	1.11	0.62 - 2.00	0.728
Urinary Incontinence	2.32	1.26 - 4.25	0.006	1.30	0.56 - 3.02	0.550
No of regular medicines	1.08	1.03 - 1.14	0.003	1.06	0.98 - 1.15	0.139

RR, relative risk. AHT, Antihypertensive. WHO-DDD, World Health Organisation Defined Daily Dose. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). *n* is smaller in final model (*n*=724) due to missing data across covariates: medication refill gaps (7), age (5), education (46), marital status (31), medical history (1), medication history (6), antihypertensive WHO-DDD (16), addition/titration of AHT (156).

Table 3 The adjusted regression models for the association between 5-day gaps in antihypertensive medication adherence and injurious falls from sensitivity analyses in 1) the propensity score adjustment analysis and 2) the negative control exposure analysis.

	Propensity Score Adjustment Model		
	aRR	**95% CI**	***p***
Adherence Gaps ≥5 days	1.17	1.03 - 1.35	0.020

RR, relative risk. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). The propensity score adjustment model analysis (n=724), used a propensity score covariate adjustment method to control for covariates listed in Table 1. Similar estimates to the primary model were observed.

Table 4 The adjusted regression models for the association between 5-day gaps in antihypertensive medication adherence and injurious falls from sensitivity analyses in 1) the propensity score adjustment analysis and 2) the negative control exposure analysis.

	Negative Control Exposure Model			Weighted Negative Control Exposure Model		
	aRR	**95% CI**	***p***	**aRR**	**95% CI**	***p***
Adherence Gaps ≥5 days	1.04	0.84 - 1.28	0.728	1.04	0.85 - 1.29	0.672

RR, relative risk. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). The estimates for the negative control exposure model (n=515), tested the association between gaps in anti-thrombotic medication adherence and injurious falls, adjusted for covariates listed in Table 1. A significant association in the negative exposure control model would indicate the presence of confounding associated with the exposure variable.

Figure Legends

Figure 1. Each 5-day gap in **antihypertensive** medication adherence was associated with a 18% increased risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). Wider confidence intervals were observed at the upper end of the graph due to the low number of participants with 6 or more 5-day gaps in antihypertensive refill behaviour.

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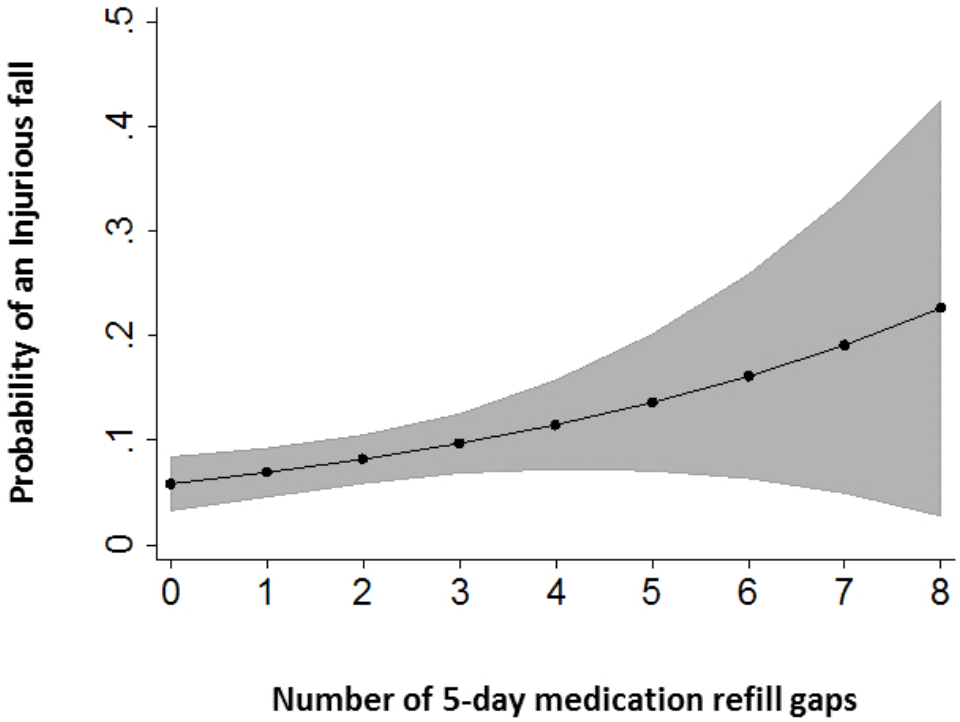

Figure 1 Each 5-day gap in antihypertensive medication adherence was associated with a 18% increased risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). Wider confidence intervals were observed at the upper end of the graph due to the low number of participants with 6 or more 5-day gaps in antihypertensive refill behaviour.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 14
		(*e*) Describe any sensitivity analyses	Page 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10
		(b) Give reasons for non-participation at each stage	Page 6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	Page 4
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Table 2

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 & 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between gaps in antihypertensive medication adherence and injurious falls in older community-dwelling adults: a prospective cohort study

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The association between gaps in antihypertensive medication adherence and injurious falls in older community-dwelling adults: a prospective cohort study

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Keywords

Injurious falls, older adults, antihypertensive medication, medication adherence, gaps in adherence

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Abstract

Objective

Growing evidence suggests that older adults are at an increased risk of injurious falls when initiating antihypertensive medication, while the evidence regarding long-term use of antihypertensive medication and the risk of falling is mixed. However, long-term users who stop and start these medications may have similar risk of falling to initial users of antihypertensive medication. Our aim was to evaluate the association between gaps in antihypertensive medication adherence and injurious falls in older (>65yrs) community-dwelling, long-term (>1yr) antihypertensive users.

Design

Prospective cohort study

Setting

Irish Community Pharmacy

Participants

Consecutive participants presenting a prescription for antihypertensive medication to 106 community pharmacies nationwide, community dwelling, over 65 years, with no evidence of cognitive impairment, taking antihypertensive medication for 1 year or longer (n=938).

Measures

Gaps in antihypertensive medication adherence were evaluated from linked dispensing records as the number of 5-day gaps between sequential supplies over the 12-month period prior to baseline. Injurious falls during follow-up were recorded via questionnaire during structured telephone interviews at 12-months.

Results

At 12-months, 8.1% (n=76) of participants reported an injurious fall requiring medical attention. The mean number of 5-day gaps in medication-refill behaviour was 1.47 *(1.58)*. In adjusted modified Poisson models 5-day medication-refill gaps at baseline was associated with a higher risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, *p*=0.024).

Conclusion

Each 5-day gap in antihypertensive refill-adherence increased the risk of self-reported injurious falls by 18%. Gaps in antihypertensive adherence may be a marker for increased injurious falls-risk. It is unknown whether adherence-interventions will reduce subsequent risk. This finding is hypothesis generating and should be replicated in similar populations.

Strengths and limitations of this study

- Prospective cohort study of a community-dwelling older recruited from community pharmacies across the Republic of Ireland.
- Objective evaluation of medication exposures and medication adherence although injurious falls was self-reported which may lead to misclassification.
- Negative control exposure analyses to account for a potential healthy-adherer effect were conducted.
- Data on some important confounders, such as such as history of previous falls, frailty and disability, and the date of falls were not available to us.

Introduction

While many studies have demonstrated the benefits of antihypertensive agents on myocardial infarction and stroke risk reduction (1-3), concerns have been raised regarding the risk of falls associated with antihypertensive medications among older adults (4, 5). Growing evidence suggests that the associated risk of injurious falls varies according to the duration of treatment (5, 6). Studies have consistently shown that older adults are at a greater risk for injurious falls or hip fractures shortly after initiating antihypertensive medications (7-12). Although the underlying mechanism is unknown, it is thought that antihypertensive medication cause or exacerbate orthostatic hypotension in the elderly resulting in poor balance, weakness, dizziness and falls (5, 13-15). The prevalence of orthostatic hypotension increases with age and uncontrolled hypertension (16), and orthostatic hypotension itself is associated with an increased risk of injurious falls (17, 18). There is also evidence that initial antihypertensive medication use is associated with orthostatic hypotension as a result of reduced cardiac output and plasma volume (19, 20).

Observational studies investigating the risk of injurious falls among long-term users of antihypertensive agents have yielded mixed results (21-28). Despite the known risks associated with treatment initiation, studies of long-term users have not considered the potential effect of medication adherence, specifically the quality of daily dose-taking behaviour of patients, known as dose-implementation (29), on risk of injurious falls. It is plausible that failure to consistently take antihypertensive medications may result in fluctuations in blood pressure, which could lead to an increased risk of falls (30). A study of electronically compiled dosing histories revealed intervals between antihypertensive doses to be prevalent. On any given day 10% of doses were omitted, with 43% of missed doses occurring during a sequence of three or more days of missed doses. Overall approximately half of patients omit doses for ≥ 3 days at least once a year (31). The quality of implementation of a medication regimen should be interpreted according to the pharmacology of the drug. During gaps in antihypertensive medication use, the pharmacological effects

on blood pressure will gradually diminish (32-34), and upon resumption of therapy patients may experience acute changes to blood pressure similar to initial use.

Our aim was to evaluate medication adherence, specifically as the quality of dose-implementation with long-term (>1 year) antihypertensive medication use and test its association with injurious falls in a cohort of community-dwelling older adults (>65 years).

Methods

Study Setting and Design

We conducted a prospective cohort study, recruiting participants from 106 community pharmacies across the Republic of Ireland between March and May 2014. Pharmacies were selected on the basis of participating in the National Pharmacy Internship Programme (NPIP). Each pharmacy recruited 15 consecutive participants presenting with a prescription for at least one medication for hypertension, aged >65 years, community-dwelling, able to speak and understand English with no evidence of cognitive impairment as judged by the pharmacist. In total, 2,231 consecutive patients were invited to participate at baseline, 1,592 (71.4%) consented to complete the baseline telephone interview and to link their pharmacy dispensing records. Participants completed a structured telephone interview with trained pharmacy interns at baseline and 12 months. This consisted of structured questionnaires at baseline and 12-months measuring participant socio-demographics, medical history and falls, based on similar questionnaires included in longitudinal studies such as the Irish Longitudinal Study of Ageing (TILDA) (35). Pharmacy interns were trained to undertake the structured telephone interviews and completed the interviews using standardised data collection forms. The data collection forms included templates for recording the date and time of telephone calls made to participants, and the structured interview. Interviews were subsequently linked to each patients' pharmacy records.

We evaluated medication adherence as the quality of dose-implementation using pharmacy records for the 12-months prior to baseline, with 5-day gaps in prescription-refill flagged as poor dose-implementation. Injurious falls were assessed via self-report at 12-month interview. Participants provided written informed consent. Ethical approval for this study was granted by the Research Ethics Committee of the Royal College of Surgeons in Ireland.

Patient involvement

No patients were involved in this study.

Inclusion/exclusion criteria

Participants completing the falls questionnaire at follow-up interview (n=1,230) were considered for inclusion. Subsequently we excluded participants reporting use of antihypertensive medication for less than 12 months and participants attending other pharmacies as their pharmacy records were not complete. Participants dispensed anticholinesterase medication or memantine during the study period, a proxy indicator of cognitive impairment, were also excluded due to poor recall of falls and associations with lower medication adherence (36-38), leaving a final sample of 938 participants. Figure 1 outlines the flow of participants through the study.

Outcome

Injurious falls were assessed during the 12-month follow-up period (April 2014 - May 2015). At 12-month follow-up interview we asked participants, “Have you fallen in the last year?” and “Did you injure yourself seriously enough to need medical treatment”. A standard definition of a fall as “an unexpected event in which participants come to rest on the ground, floor, or lower level” was used (39). Injurious falls are likely to be recalled more accurately due to the subsequent medical treatment (36).

Exposure

We evaluated medication adherence, specifically the quality of dose-implementation for the 12-month period prior to baseline (March 2013 - April 2014), by measuring the number of 5-day gaps in prescription refill from linked patient pharmacy records. Pharmacy dispensing records are an objective and indirect measure of medication adherence (40-42). We chose a 5-day gap based on literature describing the gradual decline of antihypertensive medication effect on blood pressure over three days (32-34), extending this period to five days due to the indirect method of adherence measurement, and

to allow for potential variation in antihypertensive medication pharmacology (43). The number of occasions that gaps of five days occurred between sequential supplies during the previous 12 months was evaluated at baseline. Oversupplies were credited to a maximum excess of 180 days of medication.

Covariates

Confounding factors were chosen based on known associations with falls and medication adherence behaviour. Age, gender, marital status, education level and comorbidities including depression, diabetes mellitus, rheumatoid arthritis and stroke were recorded at baseline interview (38). Parkinson's disease and urinary incontinence were identified by proxy from medication (ATC N04; ATC G04BD) (38). A meta-analysis by Woolcott et al was used to classify medication as falls-risk increasing drugs (antipsychotics, antidepressants, benzodiazepines, NSAIDs, opiates, and sedatives) from linked dispensing records (44). The number of regular medicines dispensed may also be associated with an increased falls risk (27, 45). Class of antihypertensive used may affect falls risk, for example, ACEIs and ARBs have been observed to lower the risk of falls (21, 24). Moderate (22) and high (25) doses have also been linked to an increased falls risk. Standardised doses of antihypertensive medication were determined using the World Health Organisation's Daily Defined Dose (WHO-DDD). Addition and titration of antihypertensive medication may precipitate a fall (11) and a binary variable was created to account for this during follow-up.

Statistical analysis

Descriptive statistics are presented for participant characteristics at both baseline and follow-up. Means and standard deviations are presented for continuous variables; counts and proportions for categorical variables. The association between 5-day gaps in medication-refill and injurious falls during follow-up was estimated using modified Poisson regression to obtain relative risks rather than odds ratios, which is considered more suitable when outcomes are not rare (46). Standard errors were adjusted in regression models using the Sandwich-estimator, due to potential for dependency of observations at the

pharmacy-level. Rather than selecting confounding factors for inclusion in the final model based on univariate associations, the final multivariable model was adjusted for all measured confounders.

Sensitivity analysis

Due to concerns of multivariable regression models with many covariates and a low number of outcome events we also undertook a sensitivity analysis using a propensity score covariate adjustment model. To reduce the number of confounders we estimated a Poisson model with 5-day gaps in antihypertensive prescription refills as outcome and all other covariates as predictors. The predicted value from the resultant regression equation for each observation was then used to adjust for covariates in the final modified Poisson regression model with injurious falls as outcome and number of 5-day gaps in antihypertensive prescription refill as the predictor variable (47).

Negative control analysis

Finally, a negative control exposure model was also estimated. Negative controls are a tool for detecting confounding bias in observational studies to help identify potential non-causal associations (48). In negative control tests, conditions are reproduced that cannot involve the hypothesised causal mechanism, but likely involve the same sources of bias, such as the healthy adherer bias in adherence research (48, 49). Patients with poorer medication adherence tend to have worse outcomes, leading to spurious associations in adherence research known as the healthy adherer bias (49). Negative control exposure models in particular are useful to detect confounding resulting from the healthy adherer bias, due to the ability to change the conditions by choosing an alternative medication to evaluate adherence that removes the hypothesised causal mechanism, but maintaining the potential for the healthy adherer bias. In the current study, the association between 5-day gaps in medication taking behaviour to anti-thrombotic medication and injurious falls was also estimated. Anti-thrombotics (ATC Code B01AC, B01AE, B01AF e.g. aspirin, dabigatran, rivaroxaban) were chosen due to high prevalence of use in this

sample and the lack of a theoretical association with falls. An association between gaps in anti-thrombotic medication adherence and injurious falls would indicate the presence of confounding associated with the exposure variable (50). The characteristics of the subsample may differ statistically from the entire sample (n=938) and introduce bias into the estimates of the negative control analysis. Differences in participant characteristics between those using anti-thrombotic and those not using anti-thrombotic medication was thus also evaluated using Pearsons' $\chi 2$ and *t*-tests. Based on these differences an additional weighted negative control regression analysis using inverse probability weights was undertaken. Weights were estimated as the ratio of the predicted probabilities using two probit regressions, one with and one without statistically different participant characteristic variables.

Statistical modelling was performed using Stata version 14 (StataCorp College Station, Texas, USA).

Results

The mean age of this sample was 76.1 years and 47.9% were men (n=938). The mean duration of antihypertensive therapy was 11.7 years with participants taking a mean of 2.1 different classes of antihypertensive medication. Participants reported a mean of 2.4 additional co-morbid conditions and were taking on average 6.2 regular medication. Table 1 provides a summary of participant characteristics at baseline and 12-month follow-up.

During 12-months follow-up, 8.1% (n=76) of participants reported an injurious fall requiring medical attention or treatment. At baseline the mean number of 5-day gaps in medication-refill behaviour was 1.47 *(sd 1.58)*.

Primary analysis

Table 2 details the results of the modified Poisson regression model. In the adjusted analysis, 5-day medication-refill gaps at baseline was prospectively associated with a higher risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, *p*=0.024). As demonstrated in Figure 2, each 5-day gap in antihypertensive medication refill-adherence was associated with an 18% increased risk of a self-reported injurious fall during follow-up. For participants with one 5-day gap in medication-refill compared to participants with none, the respective absolute adjusted risk of an injurious fall is 6.9% versus 5.8%, equating to an additional 11 injurious falls per 1000 patients with one 5-day gap in medication refill adherence.

Sensitivity analyses

The propensity score adjustment model analysis (n=724), used a propensity score covariate adjustment method to control for covariates listed in Table 1. The propensity score covariate adjustment model produced similar estimates (aRR 1.17, 95% CI 1.03 – 1.35, *p*=0.020) to our primary analysis.

Negative control analysis

For the negative control exposure analysis, 60% (n=566) of participants were regularly using anti-thrombotic medication. The mean number of 5-day gaps in anti-thrombotic prescription refill was 1.28 (*1.40)*. Table 3 presents the results of the negative control analysis. In multivariate modified Poisson regression analysis, adjusted for covariates, 5-day gaps in anti-thrombotic medication-refill behaviour was not associated with injurious falls (aRR 1.04, 95% CI 0.84 – 1.28, *p*=0.728). In comparison to the antihypertensive sample (n=938), the anti-thromobotic sample consisted of a statistically significant higher proportion of males, a higher rate of co-morbidities and higher rate of regular medication use. To adjust for potential bias, this subsample of 566 participants was re-weighted using inverse probability weights, estimated as the ratio of the predicted probabilities using two probit regressions, one with and one without statistically significant variables (gender, co-moribidites, regular medication use). In weighted multivariate modified Poisson regression analysis similar estimates were observed. Adjusting for covariates, 5-day gaps in anti-thrombotic medication-refill behaviour was not associated with injurious falls (aRR 1.04, 95% CI 0.85 – 1.29, *p*=0.672).

Participant attrition

There were no differences in injurious falls reported or number of medication gaps between those included the analysis compared to those lost to follow-up and excluded from the analysis. However, participants excluded due to attending other pharmacies, tended to be younger, were less likely to report a heart-attack and reported fewer co-morbidities, while patients lost to follow-up at 12 months were older and used more regular medication, which resulted in a balance of these covariates in the final analysis.

Missing data

In the complete case multivariate analysis (n=724) for the association between 5 day gaps in antihypertensive adherence and injurious, 22.8% of observations were dropped due to missing data. The largest source of missing data was due to the variable indicating addition/titration of antihypertensive medication during follow-up (n=156). This missing data was attributed to incomplete extraction of dispensing records at 12-month follow-up. Removing this variable from the final multivariate model yielded a model with a higher number of observations (n=856) and similar estimates for the association between 5 day gaps in adherence and injurious falls (aRR 1.16, 95% CI 1.02-1.31, *p*=0.019). Multiple imputation was also undertaken utilising a multivariate normal distribution, Markov Chain Monte Carlo procedure and 100 imputations. In this multiple imputation similar estimates were obtained (aRR 1.15, 95% CI 1.02-1.30, *p*=0.020).

Discussion

Principal findings

We observed an 18% increased risk of a self-reported injurious fall for each 5-day gap in antihypertensive medication refill-adherence. This equated to an additional 11 injurious falls per 1000 patients with one 5-day gap in medication refill adherence compared to patients with no gaps. This finding was statistically significant following adjustment for a large number of clinically relevant fall risk factors including age, gender, co-morbidities and fall-risk increasing medication. Furthermore, a negative control exposure model did not indicate the potential for confounding due to the healthy-adherer bias.

Findings in the context of previous literature

This is the first study to examine medication adherence, specifically the quality of dose-implementation on the risk of falls associated with antihypertensive medication use. A previous study by Berry et al identified an increased risk of falls for patients reporting lower medication adherence. They used a subjective method to evaluate medication adherence and did not differentiate adherence between drug classes (30). In contrast, we used an objective method to evaluate medication adherence and applied it to the exposure of interest, identifying that almost two-thirds of community-dwelling adults had at least one gap in antihypertensive medication-refill over 12-months. A number of observational studies have consistently identified a higher risk of falling following antihypertensive medication initiation or titration (7-12). Patients with poor medication adherence, specifically poor implementation of antihypertensive pharmacotherapy, characterised by gaps in antihypertensive medication use, may experience a gradual rise in blood pressure (32-34). Upon resumption of therapy, similar to initial use, patients may be at a greater risk for falls relative to those who do not have gaps in antihypertensive therapy. In light of the consistent evidence indicating that initiating, titrating and adding antihypertensive medication is associated with a short-term increased risk of injurious falls (7-12), patients with gaps in their adherence

to these therapies will potentially be exposed to similar pharmacological effects experienced on initiating antihypertensive medication. It has been suggested that the mechanism underlying falls risk during initiation of therapy is antihypertensive medication induced acute orthostatic hypotension (5). Orthostatic hypotension is associated with an increased risk of injurious falls (17, 18). Further research is needed to investigate if gaps in antihypertensive medication adherence may also increase orthostatic hypotension.

There are conflicting findings on the association between falls and long-term antihypertensive use. Higher doses of antihypertensive medication (22, 25), and the use of loop diuretics (23) and non-selective beta-blockers (26, 28) have been linked to falls, whereas a protective effect for the use of ACEIs and ARBs has been reported (24). Furthermore two recent studies have found no association between antihypertensive medication use and falls in older adults (21, 27). A limitation to these studies is the failure to evaluate patients' medication adherence, potentially confounding findings. Chronic use of antihypertensive medication may improve systemic and cerebral haemodynamics, and reduce orthostatic hypotension, leading to a reduction in injurious falls (17, 21). However failing to account for medication adherence in long-term users may confound the association between antihypertensive use and injurious falls. Furthermore, medication adherence is known to vary according to class of antihypertensive medication, with higher adherence associated with ACE inhibitors and ARBs, and lower adherence associated with diuretics and beta-blockers (51). These associations may be an explanatory factor for the protective effect observed for ACE inhibitors and ARBs, and the adverse effect observed for diuretics and beta-blocker on falls risk. Findings from randomized controlled trials of antihypertensive medication have reported no increase in falls risk (3, 52-54). Nonetheless, trials tend to be of healthier populations that are not readily generalizable to real world settings (55, 56). For example the recent SPRINT trial demonstrated in adults older than 75 years, that intensive blood pressure control was not associated with an increase in injurious falls (54). However the external validity of this finding is

questionable. A nationally representative longitudinal study of older adults meeting the SPRINT inclusion criteria observed a 5-fold higher rate of injurious falls than the standard care group within SPRINT during a comparable follow-up period (57). Furthermore, it is apparent that medication adherence of clinical trial participants is higher. Two-thirds of our real-world participants had at least one 5-day gap in antihypertensive medication-refill over a 12-month period compared to only half of clinical trial participants who miss three consecutive days of antihypertensive within the same time period (31).

Strengths and limitations

A strength of this study was the recruitment of community-dwelling older people from a national sample of pharmacies in Ireland, using a consecutive recruitment method. Although consecutive recruitment is a non-probabilistic method of sampling it provides structured recruitment and additional rigour, ensuring all potential participants can be enrolled. Furthermore, the convenience sample of pharmacies included in this sample are unlikely to differ significantly from other community pharmacies in the Republic of Ireland. Only a small number of community pharmacies are continually involved, with approximately 40-50% annual changeover in community pharmacies involved in the NPIP. These findings are likely to be only generalisable to those taking antihypertensive medication for longer than 1 year, and who consistently attend the same pharmacy to obtain antihypertensive medication. Participants that we excluded because of attending other pharmacies were more likely to be younger and report less co-morbidities. Additional strengths of this study include the prospective evaluation between medication-gaps (measured prior to baseline) and injurious falls (evaluated from baseline to end of follow-up), with covariates remaining relatively consistent between baseline and follow-up. However, it was not possible to fully observe the temporal association between exposure and outcome, as the date of falls was not available. There are limitations to the use of a self-report measure of injurious falls, which may result in misclassification. Ideally, falls should be recorded prospectively on a daily basis with a minimum of monthly reporting, using methods such as postcards or diaries. However, these methods

are resource intensive and are not feasible in many large-scale prospective studies (36, 39). Less frequent gathering of falls data may result in misclassification in older people due to higher likelihood of memory impairment (58). However a systematic review of studies comparing the validity of fall recall questionnaires with intensive prospective methods found falls recall to have high specificity (91-95%) and sensitivity (80-89%) in comparison to weekly postcards, or daily diaries (36). Injurious falls are often recalled with greater accuracy due to resulting negative morbidity and subsequent medical treatment (59-61). Furthermore we observed comparable rates of injurious falls to similar studies of older adults in Ireland and the UK (18, 62). Excluding participants with possible cognitive impairment and dementia may have minimized fall recall misclassification. However our methods to evaluate cognitive impairment may have resulted in misclassification due to potential under-diagnosis of patients in community settings (63). Although we excluded participants based on medication dispensed for cognitive impairment, it was not feasible during recruitment to screen all potential participants for cognitive impairment using a structured questionnaire. We also used an indirect method to evaluate medication adherence. Dispensing of medication from the pharmacy does not necessarily prove consumption (40). However, by evaluating medication-refill adherence using a gap method, we can identify definitive periods where participants had at least 5-days during which they had insufficient medication to continuously consume antihypertensive medication until obtaining a subsequent supply. The resultant misclassification of medication adherence would weaken associations between medication-refill gaps and injurious falls.

Additional strengths include the adjustment for a large number of potential confounders, including demographics, medical history and medication use. Furthermore, in comparison to other observational studies, medication use was evaluated objectively using pharmacy records, and concurrent changes to antihypertensive therapy including addition of classes and titration of doses were controlled for. Only established fall-risk increasing drugs were considered, hence only specific drugs or classes identified in

previous meta-analysis were included (44). Due to potential issues of testing a large number of predictors on a binary outcome with a low number of events in multivariate regression, a propensity score covariate adjustment model was also estimated, which did not change findings (47). The possibility for residual confounding may remain. Participants' blood pressure during the follow-up period was not measured to assess fluctuations in blood pressure. However the ability of antihypertensive drugs to lower blood pressure have been proven in clinical trials (1-3), and clinical studies have shown that withdrawal of these medications leads to a gradual rebound in blood pressure (32-34). Furthermore, the feasibility of undertaking these measurements, which would likely require daily measurements, is unlikely in large observational studies such as this. Indeed measuring patient blood pressure on a daily basis would change the medication-taking behaviour of participants, known as white-coat adherence (64, 65), which is similar to the Hawthorne effect. Some important fall-risk factors were also unmeasured such as history of previous falls, frailty and disability (38). However, a negative control exposure analysis was undertaken to evaluate the potential for residual confounding. In the negative control model no association between gaps in anti-thrombotic medication adherence and injurious falls was observed. Theoretically there should be no association and the negative control exposure model indicates potential confounding resulting from the healthy adherer bias is unlikely (48, 49).

Conclusion

An 18% increased risk of a self-reported injurious fall associated with each 5-day gap in antihypertensive medication refill-adherence was observed. Our findings should be considered as hypothesis generating and future research should attempt to fully test the temporal relationship with injurious falls. If feasible, a direct method, such as electronic dose monitoring devices, should be used to evaluate quality of dose-implementation. Clinicians reconciling the risk of falls in older patients prescribed antihypertensive medication, could use gaps in antihypertensive medication adherence as a marker to identify patient at

higher risk of injurious falls. Although further research is needed to investigate whether improving adherence to antihypertensive medication can reduce injurious falls, advising patients to consistently take antihypertensive medication will reduce cardiovascular disease risk.

Author Statement

PD, SS, PG, GC were involved in the conception and design of the study. PD and GC undertook the acquisition, and analysis of the work. PD, SS, PG, GC interpreted the data. PD, SS, PG, GC drafted the manuscript. PD, SS, PG, GC revised the manuscript and gave final approval of the version to be published. PD, SS, PG, GC agree agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflicts of Interest: None to declare

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Tables

Table 1 A summary of participant characteristics as evaluated at baseline interview and follow-up via questionnaire and via linked dispensing records (n=938)

	Baseline	Follow-up
Demographics		
Age, *mean* (SD)	76.1 (*6.1*)	77.1 (*6.1*)
Male, % (*n*)	47.9 (449)	47.9 (449)
Year on AHT meds, *mean* (SD)	11.7 (*8.9*)	12.7 (*8.9*)
Education		
Primary, % (*n*)	26.7 (250)	26.7 (250)
Secondary, % (*n*)	42.0 (394)	42.0 (394)
Third-Level, % (*n*)	26.4 (248)	26.4 (248)
Marital Status		
Married/Partner, % (*n*)	59.3 (556)	58.4 (548)
Single/Divorced/Widow, % (*n*)	37.4 (351)	39.1 (367)
Medical History		
Depression, % (*n*)	13.3 (125)	13.9 (131)
Stroke, % (*n*)	3.5 (33)	3.5 (33)
Arthritis, % (*n*)	43.7 (410)	48.1 (451)
Diabetes, % (*n*)	20.5 (192)	21.5 (202)
Morbidity Count, *mean* (SD)	2.4 (*1.6*)	2.5 (*1.7*)
Medication History		
Alpha-blocker, % (*n*)	6.7 (63)	5.2 (49)
Beta-blocker, % (*n*)	48.4 (454)	42.4 (398)
Diuretic, % (*n*)	29.6 (278)	23.8 (223)
Calcium antagonists, % (*n*)	43.9 (412)	37.5 (352)
Angiotensin inhibitors/blockers, % (*n*)	77.6 (728)	64.1 (601)
Number of AHT classes, *mean* (SD)	2.1 (*1.0*)	2.1 *(0.9*)
AHT WHO-DDD, *mean* (SD)	2.7 (*2.2*)	2.6 (*1.9*)
Antipsychotics, % (*n*)	2.8 (26)	2.0 (19)
Antidepressants, % (*n*)	15.6 (146)	13.5 (127)
Benzodiazepines, % (*n*)	9.2 (86)	7.2 (68)
NSAIDs, % (*n*)	9.1 (85)	6.0 (56)
Opiates, % (*n*)	6.2 (58)	5.7 (53)
Parkinson's disease, % (*n*)	1.1 (10)	1.3 (12)
Sedatives, % (*n*)	8.2 (77)	8.5 (80)
Urinary Incontinence, % (*n*)	5.4 (51)	5.4 (51)
Number of regular medicines, *mean* (SD)	6.2 (*3.7*)	5.9 (*4.1*)

% may not add up to 100% due to missing data. AHT=antihypertensive medication.

Table 2 The estimates, 95% confidence intervals and *p*-values for the association between 5-day gaps in antihypertensive medication adherence and injurious falls

	Crude RR	95% CI	*p*	Adj. RR	95% CI	*p*
Medication-Refill Gaps ≥5 days	1.14	1.02 - 1.28	0.023	1.18	1.02 - 1.37	0.024
Age	1.06	1.02 - 1.10	0.004	1.06	1.01- 1.12	0.029
Female gender	2.12	1.28 - 3.50	0.004	2.00	0.95 - 4.20	0.067
***Education* Primary**	Ref	-	-	-	-	-
Secondary	1.61	0.90 - 2.87	0.109	2.00	1.04 - 3.85	0.038
Third-level	1.41	0.70 - 2.83	0.331	1.54	0.66 - 3.55	0.315
***Marital Status* Married/Partner**	Ref	-	-	-	-	-
Single/Widow/Div	1.34	0.87 - 2.06	0.183	0.85	0.49 - 1.48	0.566
Depression	0.87	0.39 - 1.94	0.737	0.25	0.08 - 0.84	0.025
Stroke	0.74	0.19 - 2.90	0.666	1.01	0.18 - 5.67	0.990
Arthritis	1.51	0.95 - 2.37	0.078	0.80	0.47 - 1.38	0.426
Diabetes	0.73	0.39 - 1.35	0.312	0.71	0.35 - 1.44	0.346
Co-morbidity count	1.16	1.03 - 1.32	0.016	1.18	0.94 - 1.49	0.161
Alpha-Blocker	1.18	0.56 - 2.50	0.661	0.60	0.19 - 1.88	0.377
Beta-blocker	1.17	0.77 - 1.77	0.461	1.29	0.76 - 2.19	0.346
Diuretics	0.90	0.55 - 1.46	0.665	1.03	0.56 - 1.89	0.920
Calcium antagonists	1.02	0.68 - 1.54	0.918	1.14	0.65 - 1.98	0.653
Angiotensin inhibitors/blockers	0.73	0.45 - 1.19	0.212	0.84	0.46 - 1.54	0.576
Time since initial AHT Rx	1.01	0.99 - 1.03	0.465	1.01	0.99 - 1.03	0.400
Antihypertensive WHO-DDD	0.97	0.89 - 1.06	0.487	1.00	0.86 - 1.16	0.997
Addition/titration of AHT	1.67	0.97 - 2.90	0.064	1.87	0.99 - 3.55	0.054
Antipsychotics	0.94	0.23 - 3.80	0.933	1.52	0.34 - 6.75	0.581
Antidepressants	1.55	0.92 - 2.63	0.102	1.80	0.87 - 3.74	0.113
Benzodiazepines	2.03	1.20 - 3.44	0.008	1.29	0.62 - 2.68	0.493
NSAIDs	0.55	0.22 - 1.39	0.208	0.52	0.19 - 1.44	0.207
Opiates	2.28	1.27 - 4.09	0.006	2.00	1.06 - 3.76	0.032
Parkinsonian Drugs	2.49	0.70 - 8.85	0.158	2.97	0.44 - 20.0	0.263
Hypnotics and Sedatives	1.31	0.69 - 2.46	0.408	1.11	0.62 - 2.00	0.728
Urinary Incontinence	2.32	1.26 - 4.25	0.006	1.30	0.56 - 3.02	0.550
No of regular medicines	1.08	1.03 - 1.14	0.003	1.06	0.98 - 1.15	0.139

RR, relative risk. AHT, Antihypertensive. WHO-DDD, World Health Organisation Defined Daily Dose. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). *n* is smaller in final model (*n*=724) due to missing data across covariates: medication refill gaps (7), age (5), education (46), marital status (31), medical history (1), medication history (6), antihypertensive WHO-DDD (16), addition/titration of AHT (156).

Table 3 The adjusted regression models for the association between 5-day gaps in antihypertensive medication adherence and injurious falls from sensitivity analyses in 1) the propensity score adjustment analysis and 2) the negative control exposure analysis.

	Negative Control Exposure Model			Weighted Negative Control Exposure Model		
	aRR	**95% CI**	***p***	**aRR**	**95% CI**	***p***
Adherence Gaps ≥5 days	1.04	0.84 - 1.28	0.728	1.04	0.85 - 1.29	0.672

RR, relative risk. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). The estimates for the negative control exposure model (n=515), tested the association between gaps in anti-thrombotic medication adherence and injurious falls, adjusted for covariates listed in Table 1. A significant association in the negative exposure control model would indicate the presence of confounding associated with the exposure variable.

Figure Legends

Figure 1. Flow of participants through the study. AHT=Antihypertensive.

Figure 2. Each 5-day gap in antihypertensive medication adherence was associated with an 18% increased risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). Wider confidence intervals were observed at the upper end of the graph due to the low number of participants with 6 or more 5-day gaps in antihypertensive refill behaviour.

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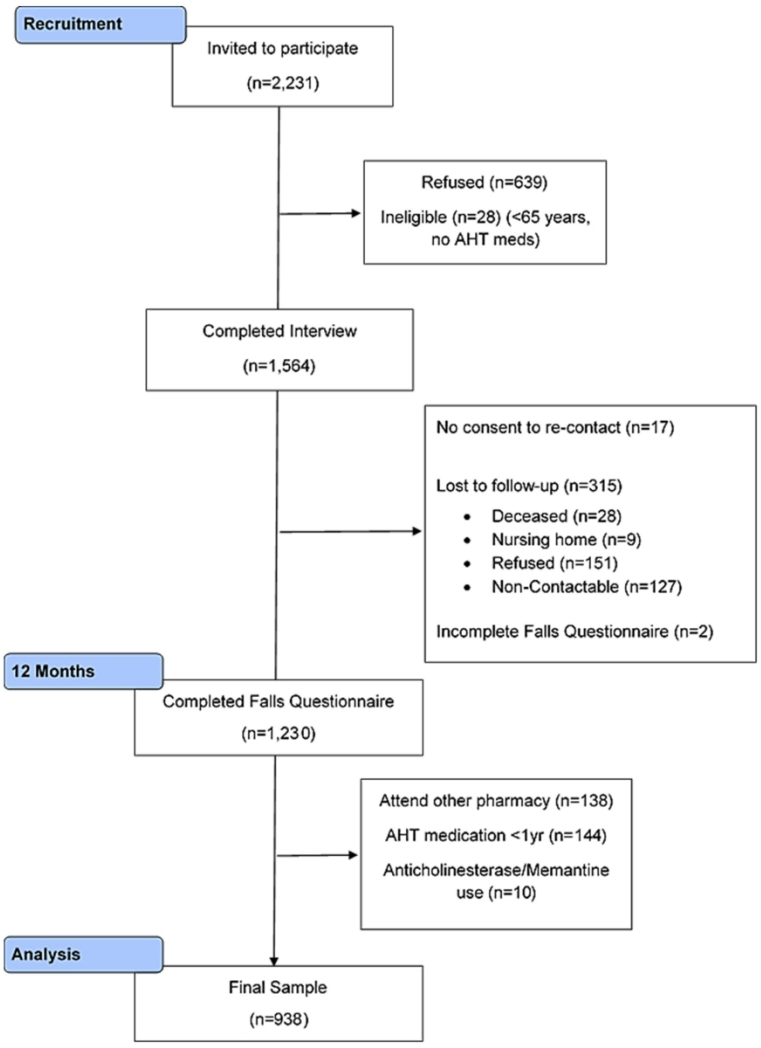

Figure 1. Flow of participants through the study. AHT=Antihypertensive.

190x275mm (300 x 300 DPI)

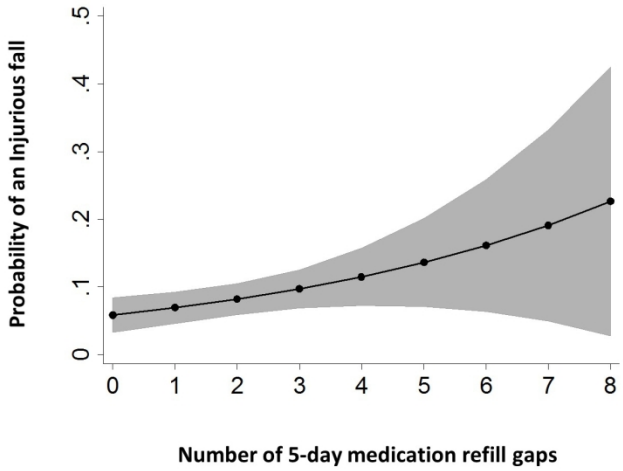

Figure 2. Each 5-day gap in antihypertensive medication adherence was associated with an 18% increased risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). Wider confidence intervals were observed at the upper end of the graph due to the low number of participants with 6 or more 5-day gaps in antihypertensive refill behaviour.

149x199mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 14
		(*e*) Describe any sensitivity analyses	Page 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10
		(b) Give reasons for non-participation at each stage	Page 6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	Page 4
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Table 2

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 & 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between gaps in antihypertensive medication adherence and injurious falls in older community-dwelling adults: a prospective cohort study

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The association between gaps in antihypertensive medication adherence and injurious falls in older community-dwelling adults: a prospective cohort study

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Word Count 3942

Abstract

Objective

Growing evidence suggests that older adults are at an increased risk of injurious falls when initiating antihypertensive medication, while the evidence regarding long-term use of antihypertensive medication and the risk of falling is mixed. However, long-term users who stop and start these medications may have similar risk of falling to initial users of antihypertensive medication. Our aim was to evaluate the association between gaps in antihypertensive medication adherence and injurious falls in older (>65yrs) community-dwelling, long-term (>1yr) antihypertensive users.

Design

Prospective cohort study

Setting

Irish Community Pharmacy

Participants

Consecutive participants presenting a prescription for antihypertensive medication to 106 community pharmacies nationwide, community dwelling, over 65 years, with no evidence of cognitive impairment, taking antihypertensive medication for 1 year or longer (n=938).

Measures

Gaps in antihypertensive medication adherence were evaluated from linked dispensing records as the number of 5-day gaps between sequential supplies over the 12-month period prior to baseline. Injurious falls during follow-up were recorded via questionnaire during structured telephone interviews at 12-months.

Results

At 12-months, 8.1% (n=76) of participants reported an injurious fall requiring medical attention. The mean number of 5-day gaps in medication-refill behaviour was 1.47 *(1.58)*. In adjusted modified Poisson models 5-day medication-refill gaps at baseline was associated with a higher risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, *p*=0.024).

Conclusion

Each 5-day gap in antihypertensive refill-adherence increased the risk of self-reported injurious falls by 18%. Gaps in antihypertensive adherence may be a marker for increased injurious falls-risk. It is unknown whether adherence-interventions will reduce subsequent risk. This finding is hypothesis generating and should be replicated in similar populations.

Strengths and limitations of this study

- Prospective cohort study of a community-dwelling older recruited from community pharmacies across the Republic of Ireland.
- Objective evaluation of medication exposures and medication adherence although injurious falls was self-reported which may lead to misclassification.
- Negative control exposure analyses to account for a potential healthy-adherer effect were conducted.
- Data on some important confounders, such as such as history of previous falls, frailty and disability, and the date of falls were not available to us.

Introduction

While many studies have demonstrated the benefits of antihypertensive agents on myocardial infarction and stroke risk reduction (1-3), concerns have been raised regarding the risk of falls associated with antihypertensive medications among older adults (4, 5). Growing evidence suggests that the associated risk of injurious falls varies according to the duration of treatment (5, 6). Studies have consistently shown that older adults are at a greater risk for injurious falls or hip fractures shortly after initiating antihypertensive medications (7-12). Although the underlying mechanism is unknown, it is thought that antihypertensive medication cause or exacerbate orthostatic hypotension in the elderly resulting in poor balance, weakness, dizziness and falls (5). The prevalence of orthostatic hypotension increases with age and uncontrolled hypertension (13), and orthostatic hypotension itself is associated with an increased risk of injurious falls (14, 15).

Observational studies investigating the risk of injurious falls among long-term users of antihypertensive agents have yielded mixed results (16-23). Despite the known risks associated with treatment initiation, studies of long-term users have not considered the potential effect of medication adherence, specifically the quality of daily dose-taking behaviour of patients, known as dose-implementation (24), on risk of injurious falls. It is plausible that failure to consistently take antihypertensive medications may result in fluctuations in blood pressure, which could lead to an increased risk of falls (25). A study of electronically compiled dosing histories revealed intervals between antihypertensive doses to be prevalent. On any given day 10% of doses were omitted, with 43% of missed doses occurring during a sequence of three or more days of missed doses. Overall approximately half of patients omit doses for ≥ 3 days at least once a year (26). The quality of implementation of a medication regimen should be interpreted according to the pharmacology of the drug. During gaps in antihypertensive medication use, the pharmacological effects on blood pressure will gradually diminish (27-29), and upon resumption of therapy patients may experience acute changes to blood pressure similar to initial use.

Our aim was to evaluate medication adherence, specifically as the quality of dose-implementation with long-term (>1 year) antihypertensive medication use and test its association with injurious falls in a cohort of community-dwelling older adults (>65 years).

Methods

Study Setting and Design

We conducted a prospective cohort study, recruiting participants from 106 community pharmacies across the Republic of Ireland between March and May 2014. Pharmacies were selected on the basis of participating in the National Pharmacy Internship Programme (NPIP). Each pharmacy recruited 15 consecutive participants presenting with a prescription for at least one medication for hypertension, aged >65 years, community-dwelling, able to speak and understand English with no evidence of cognitive impairment as judged by the pharmacist. In total, 2,231 consecutive patients were invited to participate at baseline, 1,592 (71.4%) consented to complete the baseline telephone interview and to link their pharmacy dispensing records. Participants completed a structured telephone interview with trained pharmacy interns at baseline and 12 months. This consisted of structured questionnaires at baseline and 12-months measuring participant socio-demographics, medical history and falls, based on similar questionnaires included in longitudinal studies such as the Irish Longitudinal Study of Ageing (TILDA) (30). Pharmacy interns were trained to undertake the structured telephone interviews and completed the interviews using standardised data collection forms. The data collection forms included templates for recording the date and time of telephone calls made to participants, and the structured interview. Interviews were subsequently linked to each patients' pharmacy records.

We evaluated medication adherence as the quality of dose-implementation using pharmacy records for the 12-months prior to baseline, with 5-day gaps in prescription-refill flagged as poor dose-implementation. Injurious falls were assessed via self-report at 12-month interview. Participants provided written informed consent. Ethical approval for this study was granted by the Research Ethics Committee of the Royal College of Surgeons in Ireland.

Patient involvement

No patients were involved in this study.

Inclusion/exclusion criteria

Participants completing the falls questionnaire at follow-up interview (n=1,230) were considered for inclusion. Subsequently we excluded participants reporting use of antihypertensive medication for less than 12 months and participants attending other pharmacies as their pharmacy records were not complete. Participants dispensed anticholinesterase medication or memantine during the study period, a proxy indicator of cognitive impairment, were also excluded due to poor recall of falls and associations with lower medication adherence (31-33), leaving a final sample of 938 participants. Figure 1 outlines the flow of participants through the study.

Outcome

Injurious falls were assessed during the 12-month follow-up period (April 2014 - May 2015). At 12-month follow-up interview we asked participants, “Have you fallen in the last year?” and “Did you injure yourself seriously enough to need medical treatment”. A standard definition of a fall as “an unexpected event in which participants come to rest on the ground, floor, or lower level” was used (34). Injurious falls are likely to be recalled more accurately due to the subsequent medical treatment (31).

Exposure

We evaluated medication adherence, specifically the quality of dose-implementation for the 12-month period prior to baseline (March 2013 - April 2014), by measuring the number of 5-day gaps in prescription refill from linked patient pharmacy records. Pharmacy dispensing records are an objective and indirect measure of medication adherence (35, 36). We chose a 5-day gap based on literature describing the gradual decline of antihypertensive medication effect on blood pressure over three days (27-29), extending this period to five days due to the indirect method of adherence measurement, and

to allow for potential variation in antihypertensive medication pharmacology (37). The number of occasions that gaps of five days occurred between sequential supplies during the previous 12 months was evaluated at baseline. Oversupplies were credited to a maximum excess of 180 days of medication.

Covariates

Confounding factors were chosen based on known associations with falls and medication adherence behaviour. Age, gender, marital status, education level and comorbidities including depression, diabetes mellitus, rheumatoid arthritis and stroke were recorded at baseline interview (33). Parkinson's disease and urinary incontinence were identified by proxy from medication (ATC N04; ATC G04BD) (33). A meta-analysis by Woolcott et al was used to classify medication as falls-risk increasing drugs (antipsychotics, antidepressants, benzodiazepines, NSAIDs, opiates, and sedatives) from linked dispensing records (38). The number of regular medicines dispensed may also be associated with an increased falls risk (22). Class of antihypertensive used may affect falls risk, for example, ACEIs and ARBs have been observed to lower the risk of falls (16, 19). Moderate (17) and high (20) doses have also been linked to an increased falls risk. Standardised doses of antihypertensive medication were determined using the World Health Organisation's Daily Defined Dose (WHO-DDD). Addition and titration of antihypertensive medication may precipitate a fall (11) and a binary variable was created to account for this during follow-up.

Statistical analysis

Descriptive statistics are presented for participant characteristics at both baseline and follow-up. Means and standard deviations are presented for continuous variables; counts and proportions for categorical variables. The association between 5-day gaps in medication-refill and injurious falls during follow-up was estimated using modified Poisson regression to obtain relative risks rather than odds ratios, which is considered more suitable when outcomes are not rare (39). Standard errors were adjusted in regression models using the Sandwich-estimator, due to potential for dependency of observations at the

pharmacy-level. Rather than selecting confounding factors for inclusion in the final model based on univariate associations, the final multivariable model was adjusted for all measured confounders.

Sensitivity analysis

Due to concerns of multivariate regression models with many covariates and a low number of outcome events we also undertook a sensitivity analysis using a propensity score covariate adjustment model. To reduce the number of confounders we estimated a Poisson model with 5-day gaps in antihypertensive prescription refills as outcome and all other covariates as predictors. The predicted value from the resultant regression equation for each observation was then used to adjust for covariates in the final modified Poisson regression model with injurious falls as outcome and number of 5-day gaps in antihypertensive prescription refill as the predictor variable (40).

Negative control analysis

Finally, a negative control exposure model was also estimated. Negative controls are a tool for detecting confounding bias in observational studies to help identify potential non-causal associations (41). In negative control tests, conditions are reproduced that cannot involve the hypothesised causal mechanism, but likely involve the same sources of bias, such as the healthy adherer bias in adherence research (41, 42). Patients with poorer medication adherence tend to have worse outcomes, leading to spurious associations in adherence research known as the healthy adherer bias (42). Negative control exposure models in particular are useful to detect confounding resulting from the healthy adherer bias, due to the ability to change the conditions by choosing an alternative medication to evaluate adherence that removes the hypothesised causal mechanism, but maintaining the potential for the healthy adherer bias. In the current study, the association between 5-day gaps in medication taking behaviour to anti-thrombotic medication and injurious falls was also estimated. Anti-thrombotics (ATC Code B01AC, B01AE, B01AF e.g. aspirin, dabigatran, rivaroxaban) were chosen due to high prevalence of use in this

sample and the lack of a theoretical association with falls. An association between gaps in anti-thrombotic medication adherence and injurious falls would indicate the presence of confounding associated with the exposure variable (43). The characteristics of the subsample may differ statistically from the entire sample (n=938) and introduce bias into the estimates of the negative control analysis. Differences in participant characteristics between those using anti-thrombotic and those not using anti-thrombotic medication was thus also evaluated using Pearsons' $\chi 2$ and *t*-tests. Based on these differences an additional weighted negative control regression analysis using inverse probability weights was undertaken. Weights were estimated as the ratio of the predicted probabilities using two probit regressions, one with and one without statistically different participant characteristic variables.

Statistical modelling was performed using Stata version 14 (StataCorp College Station, Texas, USA).

Results

The mean age of this sample was 76.1 years and 47.9% were men (n=938). The mean duration of antihypertensive therapy was 11.7 years with participants taking a mean of 2.1 different classes of antihypertensive medication. Participants reported a mean of 2.4 additional co-morbid conditions and were taking on average 6.2 regular medication. Table 1 provides a summary of participant characteristics at baseline and 12-month follow-up.

During 12-months follow-up, 8.1% (n=76) of participants reported an injurious fall requiring medical attention or treatment. At baseline the mean number of 5-day gaps in medication-refill behaviour was 1.47 *(sd 1.58)*.

Primary analysis

Table 2 details the results of the modified Poisson regression model. In the adjusted analysis, 5-day medication-refill gaps at baseline were prospectively associated with a higher risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, *p*=0.024). As demonstrated in Figure 2, each 5-day gap in antihypertensive medication refill-adherence was associated with an 18% increased risk of a self-reported injurious fall during follow-up. For participants with one 5-day gap in medication-refill compared to participants with none, the respective absolute adjusted risk of an injurious fall is 6.9% versus 5.8%, equating to an additional 11 injurious falls per 1000 patients with one 5-day gap in medication refill adherence.

Sensitivity analyses

The propensity score adjustment model analysis (n=724), used a propensity score covariate adjustment method to control for covariates listed in Table 1. The propensity score covariate adjustment model produced similar estimates (aRR 1.17, 95% CI 1.03 – 1.35, *p*=0.020) to our primary analysis.

Negative control analysis

For the negative control exposure analysis, 60% (n=566) of participants were regularly using anti-thrombotic medication. The mean number of 5-day gaps in anti-thrombotic prescription refill was 1.28 (*1.40)*. Table 3 presents the results of the negative control analysis. In multivariate modified Poisson regression analysis, adjusted for covariates, 5-day gaps in anti-thrombotic medication-refill behaviour were not associated with injurious falls (aRR 1.04, 95% CI 0.84 – 1.28, *p*=0.728). In comparison to the antihypertensive sample (n=938), the anti-thromobotic sample consisted of a statistically significant higher proportion of males, a higher rate of co-morbidities and higher rate of regular medication use. To adjust for potential bias, this subsample of 566 participants was re-weighted using inverse probability weights, estimated as the ratio of the predicted probabilities using two probit regressions, one with and one without statistically significant variables (gender, co-moribidites, regular medication use). In weighted multivariate modified Poisson regression analysis similar estimates were observed. Adjusting for covariates, 5-day gaps in anti-thrombotic medication-refill behaviour were not associated with injurious falls (aRR 1.04, 95% CI 0.85 – 1.29, *p*=0.672).

Participant attrition

There were no differences in injurious falls reported or number of medication gaps between those included in the analysis compared to those lost to follow-up and excluded from the analysis. However, participants excluded due to attending other pharmacies, tended to be younger, were less likely to report a heart-attack and reported fewer co-morbidities, while patients lost to follow-up at 12 months were older and used more regular medication, which resulted in a balance of these covariates in the final analysis.

Missing data

In the complete case multivariate analysis (n=724) for the association between 5 day gaps in antihypertensive adherence and injurious, 22.8% of observations were dropped due to missing data. The largest source of missing data was due to the variable indicating addition/titration of antihypertensive medication during follow-up (n=156). This missing data was attributed to incomplete extraction of dispensing records at 12-month follow-up. Removing this variable from the final multivariate model yielded a model with a higher number of observations (n=856) and similar estimates for the association between 5 day gaps in adherence and injurious falls (aRR 1.16, 95% CI 1.02-1.31, *p*=0.019). Multiple imputation was also undertaken utilising a multivariate normal distribution, Markov Chain Monte Carlo procedure and 100 imputations. In this multiple imputation similar estimates were obtained (aRR 1.15, 95% CI 1.02-1.30, *p*=0.020).

Discussion

Principal findings

We observed an 18% increased risk of a self-reported injurious fall for each 5-day gap in antihypertensive medication refill-adherence. This equated to an additional 11 injurious falls per 1000 patients with one 5-day gap in medication refill adherence compared to patients with no gaps. This finding was statistically significant following adjustment for a large number of clinically relevant fall risk factors including age, gender, co-morbidities and fall-risk increasing medication. Furthermore, a negative control exposure model did not indicate the potential for confounding due to the healthy-adherer bias.

Findings in the context of previous literature

This is the first study to examine medication adherence, specifically the quality of dose-implementation on the risk of falls associated with antihypertensive medication use. A previous study by Berry et al identified an increased risk of falls for patients reporting lower medication adherence. They used a subjective method to evaluate medication adherence and did not differentiate adherence between drug classes (25). In contrast, we used an objective method to evaluate medication adherence and applied it to the exposure of interest, identifying that almost two-thirds of community-dwelling adults had at least one gap in antihypertensive medication-refill over 12-months. A number of observational studies have consistently identified a higher risk of falling following antihypertensive medication initiation or titration (7-12). Patients with poor medication adherence, specifically poor implementation of antihypertensive pharmacotherapy, characterised by gaps in antihypertensive medication use, may experience a gradual rise in blood pressure (27-29). Upon resumption of therapy, similar to initial use, patients may be at a greater risk for falls relative to those who do not have gaps in antihypertensive therapy. In light of the consistent evidence indicating that initiating, titrating and adding antihypertensive medication is

associated with a short-term increased risk of injurious falls (7-12), patients with gaps in their adherence to these therapies will potentially be exposed to similar pharmacological effects experienced on initiating antihypertensive medication. It has been suggested that the mechanism underlying falls risk during initiation of therapy is antihypertensive medication induced acute orthostatic hypotension (5). Orthostatic hypotension is associated with an increased risk of injurious falls (14, 15). Further research is needed to investigate if gaps in antihypertensive medication adherence may also increase orthostatic hypotension.

There are conflicting findings on the association between falls and long-term antihypertensive use. Higher doses of antihypertensive medication (17, 20), and the use of loop diuretics (18) and non-selective beta-blockers (21, 23) have been linked to falls, whereas a protective effect for the use of ACEIs and ARBs has been reported (19). Furthermore two recent studies have found no association between antihypertensive medication use and falls in older adults (16, 22). A limitation to these studies is the failure to evaluate patients' medication adherence, potentially confounding findings. Chronic use of antihypertensive medication may improve systemic and cerebral haemodynamics, and reduce orthostatic hypotension, leading to a reduction in injurious falls (14, 16). However failing to account for medication adherence in long-term users may confound the association between antihypertensive use and injurious falls. Furthermore, medication adherence is known to vary according to class of antihypertensive medication, with higher adherence associated with ACE inhibitors and ARBs, and lower adherence associated with diuretics and beta-blockers (44). These associations may be an explanatory factor for the protective effect observed for ACE inhibitors and ARBs, and the adverse effect observed for diuretics and beta-blocker on falls risk. Findings from randomized controlled trials of antihypertensive medication have reported no increase in falls risk (3, 45-47). Nonetheless, trials tend to be of healthier populations that are not readily generalizable to real world settings (48). For example the recent SPRINT trial demonstrated in adults older than 75 years, that intensive blood pressure control

was not associated with an increase in injurious falls (47). However the external validity of this finding is questionable. A nationally representative longitudinal study of older adults meeting the SPRINT inclusion criteria observed a 5-fold higher rate of injurious falls than the standard care group within SPRINT during a comparable follow-up period (49). Furthermore, it is apparent that medication adherence of clinical trial participants is higher. Two-thirds of our real-world participants had at least one 5-day gap in antihypertensive medication-refill over a 12-month period compared to only half of clinical trial participants who miss three consecutive days of antihypertensive within the same time period (26).

Strengths and limitations

A strength of this study was the recruitment of community-dwelling older people from a national sample of pharmacies in Ireland, using a consecutive recruitment method. Although consecutive recruitment is a non-probabilistic method of sampling it provides structured recruitment and additional rigour, ensuring all potential participants can be enrolled. Furthermore, the convenience sample of pharmacies included in this sample are unlikely to differ significantly from other community pharmacies in the Republic of Ireland. Only a small number of community pharmacies are continually involved in the NPIP, with approximately 40-50% annual changeover in community pharmacies involved in the NPIP. These findings are likely to be only generalisable to those taking antihypertensive medication for longer than 1 year, and who consistently attend the same pharmacy to obtain antihypertensive medication. Participants that we excluded because of attending other pharmacies were more likely to be younger and report less co-morbidities. Additional strengths of this study include the prospective evaluation between medication-gaps (measured prior to baseline) and injurious falls (evaluated from baseline to end of follow-up), with covariates remaining relatively consistent between baseline and follow-up. However, it was not possible to fully observe the temporal association between exposure and outcome, as the date of falls was not available. There are limitations to the use of a self-report measure of injurious falls, which may result in misclassification. Ideally, falls should be recorded prospectively on a

daily basis with a minimum of monthly reporting, using methods such as postcards or diaries. However, these methods are resource intensive and are not feasible in many large-scale prospective studies (31). Less frequent gathering of falls data may result in misclassification in older people due to higher likelihood of memory impairment. However a systematic review of studies comparing the validity of fall recall questionnaires with intensive prospective methods found falls recall to have high specificity (91-95%) and sensitivity (80-89%) in comparison to weekly postcards, or daily diaries (31). Injurious falls are often recalled with greater accuracy due to resulting negative morbidity and subsequent medical treatment (50). Furthermore we observed a comparable rate of injurious falls to a similar study of older adults in Ireland (15). Excluding participants with possible cognitive impairment and dementia may have minimized fall recall misclassification. However our methods to evaluate cognitive impairment may have resulted in misclassification due to potential under-diagnosis of patients in community settings (51). Although we excluded participants based on medication dispensed for cognitive impairment, it was not feasible during recruitment to screen all potential participants for cognitive impairment using a structured questionnaire. We also used an indirect method to evaluate medication adherence. Dispensing of medication from the pharmacy does not necessarily prove consumption (35). However, by evaluating medication-refill adherence using a gap method, we can identify definitive periods where participants had at least 5-days during which they had insufficient medication to continuously consume antihypertensive medication until obtaining a subsequent supply. The resultant misclassification of medication adherence would weaken associations between medication-refill gaps and injurious falls.

Additional strengths include the adjustment for a large number of potential confounders, including demographics, medical history and medication use. Furthermore, in comparison to other observational studies, medication use was evaluated objectively using pharmacy records, and concurrent changes to antihypertensive therapy including addition of classes and titration of doses were controlled for. Only established fall-risk increasing drugs were considered, hence only specific drugs or classes identified in

previous meta-analysis were included (38). Due to potential issues of testing a large number of predictors on a binary outcome with a low number of events in multivariate regression, a propensity score covariate adjustment model was also estimated, which did not change findings (40). The possibility for residual confounding may remain. Participants' blood pressure during the follow-up period was not measured to assess fluctuations in blood pressure. However the ability of antihypertensive drugs to lower blood pressure have been proven in clinical trials (1-3), and clinical studies have shown that withdrawal of these medications leads to a gradual rebound in blood pressure (27-29). Furthermore, the feasibility of undertaking these measurements, which would likely require daily measurements, is unlikely in large observational studies such as this. Indeed measuring patient blood pressure on a daily basis would change the medication-taking behaviour of participants, known as white-coat adherence, which is similar to the Hawthorne effect. Some important fall-risk factors were also unmeasured such as history of previous falls, frailty and disability (33). However, a negative control exposure analysis was undertaken to evaluate the potential for residual confounding. In the negative control model no association between gaps in anti-thrombotic medication adherence and injurious falls was observed. Theoretically there should be no association and the negative control exposure model indicates potential confounding resulting from the healthy adherer bias is unlikely (41, 42).

Conclusion

An 18% increased risk of a self-reported injurious fall associated with each 5-day gap in antihypertensive medication refill-adherence was observed. Our findings should be considered as hypothesis generating and future research should attempt to fully test the temporal relationship with injurious falls. If feasible, a direct method, such as electronic dose monitoring devices, should be used to evaluate quality of dose-implementation. Clinicians reconciling the risk of falls in older patients prescribed antihypertensive medication, could use gaps in antihypertensive medication adherence as a marker to identify patient at higher risk of injurious falls. Although further research is needed to investigate whether improving

adherence to antihypertensive medication can reduce injurious falls, advising patients to consistently take antihypertensive medication will reduce cardiovascular disease risk.

Author Statement

PD, SS, PG, GC were involved in the conception and design of the study. PD and GC undertook the acquisition, and analysis of the work. PD, SS, PG, GC interpreted the data. PD, SS, PG, GC drafted the manuscript. PD, SS, PG, GC revised the manuscript and gave final approval of the version to be published. PD, SS, PG, GC agree agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflicts of Interest: None to declare

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Data sharing statement No additional data available.

Tables

Table 1 A summary of participant characteristics as evaluated at baseline interview and follow-up via questionnaire and via linked dispensing records (n=938)

	Baseline	Follow-up
Demographics		
Age, *mean* (SD)	76.1 (*6.1*)	77.1 (*6.1*)
Male, % (*n*)	47.9 (449)	47.9 (449)
Year on AHT meds, *mean* (SD)	11.7 (*8.9*)	12.7 (*8.9*)
Education		
Primary, % (*n*)	26.7 (250)	26.7 (250)
Secondary, % (*n*)	42.0 (394)	42.0 (394)
Third-Level, % (*n*)	26.4 (248)	26.4 (248)
Marital Status		
Married/Partner, % (*n*)	59.3 (556)	58.4 (548)
Single/Divorced/Widow, % (*n*)	37.4 (351)	39.1 (367)
Medical History		
Depression, % (*n*)	13.3 (125)	13.9 (131)
Stroke, % (*n*)	3.5 (33)	3.5 (33)
Arthritis, % (*n*)	43.7 (410)	48.1 (451)
Diabetes, % (*n*)	20.5 (192)	21.5 (202)
Morbidity Count, *mean* (SD)	2.4 (*1.6*)	2.5 (*1.7*)
Medication History		
Alpha-blocker, % (*n*)	6.7 (63)	5.2 (49)
Beta-blocker, % (*n*)	48.4 (454)	42.4 (398)
Diuretic, % (*n*)	29.6 (278)	23.8 (223)
Calcium antagonists, % (*n*)	43.9 (412)	37.5 (352)
Angiotensin inhibitors/blockers, % (*n*)	77.6 (728)	64.1 (601)
Number of AHT classes, *mean* (SD)	2.1 (*1.0*)	2.1 *(0.9*)
AHT WHO-DDD, *mean* (SD)	2.7 (*2.2*)	2.6 (*1.9*)
Antipsychotics, % (*n*)	2.8 (26)	2.0 (19)
Antidepressants, % (*n*)	15.6 (146)	13.5 (127)
Benzodiazepines, % (*n*)	9.2 (86)	7.2 (68)
NSAIDs, % (*n*)	9.1 (85)	6.0 (56)
Opiates, % (*n*)	6.2 (58)	5.7 (53)
Parkinson's disease, % (*n*)	1.1 (10)	1.3 (12)
Sedatives, % (*n*)	8.2 (77)	8.5 (80)
Urinary Incontinence, % (*n*)	5.4 (51)	5.4 (51)
Number of regular medicines, *mean* (SD)	6.2 (*3.7*)	5.9 (*4.1*)

% may not add up to 100% due to missing data. AHT=antihypertensive medication.

Table 2 The estimates, 95% confidence intervals and *p*-values for the association between 5-day gaps in antihypertensive medication adherence and injurious falls

	Crude RR	95% CI	*p*	Adj. RR	95% CI	*p*
Medication-Refill Gaps ≥5 days	1.14	1.02 - 1.28	0.023	1.18	1.02 - 1.37	0.024
Age	1.06	1.02 - 1.10	0.004	1.06	1.01- 1.12	0.029
Female gender	2.12	1.28 - 3.50	0.004	2.00	0.95 - 4.20	0.067
***Education* Primary**	Ref	-	-	-	-	-
Secondary	1.61	0.90 - 2.87	0.109	2.00	1.04 - 3.85	0.038
Third-level	1.41	0.70 - 2.83	0.331	1.54	0.66 - 3.55	0.315
***Marital Status* Married/Partner**	Ref	-	-	-	-	-
Single/Widow/Div	1.34	0.87 - 2.06	0.183	0.85	0.49 - 1.48	0.566
Depression	0.87	0.39 - 1.94	0.737	0.25	0.08 - 0.84	0.025
Stroke	0.74	0.19 - 2.90	0.666	1.01	0.18 - 5.67	0.990
Arthritis	1.51	0.95 - 2.37	0.078	0.80	0.47 - 1.38	0.426
Diabetes	0.73	0.39 - 1.35	0.312	0.71	0.35 - 1.44	0.346
Co-morbidity count	1.16	1.03 - 1.32	0.016	1.18	0.94 - 1.49	0.161
Alpha-Blocker	1.18	0.56 - 2.50	0.661	0.60	0.19 - 1.88	0.377
Beta-blocker	1.17	0.77 - 1.77	0.461	1.29	0.76 - 2.19	0.346
Diuretics	0.90	0.55 - 1.46	0.665	1.03	0.56 - 1.89	0.920
Calcium antagonists	1.02	0.68 - 1.54	0.918	1.14	0.65 - 1.98	0.653
Angiotensin inhibitors/blockers	0.73	0.45 - 1.19	0.212	0.84	0.46 - 1.54	0.576
Time since initial AHT Rx	1.01	0.99 - 1.03	0.465	1.01	0.99 - 1.03	0.400
Antihypertensive WHO-DDD	0.97	0.89 - 1.06	0.487	1.00	0.86 - 1.16	0.997
Addition/titration of AHT	1.67	0.97 - 2.90	0.064	1.87	0.99 - 3.55	0.054
Antipsychotics	0.94	0.23 - 3.80	0.933	1.52	0.34 - 6.75	0.581
Antidepressants	1.55	0.92 - 2.63	0.102	1.80	0.87 - 3.74	0.113
Benzodiazepines	2.03	1.20 - 3.44	0.008	1.29	0.62 - 2.68	0.493
NSAIDs	0.55	0.22 - 1.39	0.208	0.52	0.19 - 1.44	0.207
Opiates	2.28	1.27 - 4.09	0.006	2.00	1.06 - 3.76	0.032
Parkinsonian Drugs	2.49	0.70 - 8.85	0.158	2.97	0.44 - 20.0	0.263
Hypnotics and Sedatives	1.31	0.69 - 2.46	0.408	1.11	0.62 - 2.00	0.728
Urinary Incontinence	2.32	1.26 - 4.25	0.006	1.30	0.56 - 3.02	0.550
No of regular medicines	1.08	1.03 - 1.14	0.003	1.06	0.98 - 1.15	0.139

RR, relative risk. AHT, Antihypertensive. WHO-DDD, World Health Organisation Defined Daily Dose. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). *n* is smaller in final model (*n*=724) due to missing data across covariates: medication refill gaps (7), age (5), education (46), marital status (31), medical history (1), medication history (6), antihypertensive WHO-DDD (16), addition/titration of AHT (156).

Table 3 The adjusted regression models for the association between 5-day gaps in antihypertensive medication adherence and injurious falls from sensitivity analyses in 1) the negative control exposure analysis and 2) the weighted negative control exposure analysis.

	Negative Control Exposure Model			Weighted Negative Control Exposure Model		
	aRR	**95% CI**	***p***	**aRR**	**95% CI**	***p***
Adherence Gaps ≥5 days	1.04	0.84 - 1.28	0.728	1.04	0.85 - 1.29	0.672

RR, relative risk. Modified Poisson regression with robust standard errors was used to estimate relative risks. Standard errors were adjusted for 104 clusters (pharmacy level). The estimates for the negative control exposure model (n=515), tested the association between gaps in anti-thrombotic medication adherence and injurious falls, adjusted for covariates listed in Table 1. A significant association in the negative exposure control model would indicate the presence of confounding associated with the exposure variable.

Figure Legends

Figure 1. Flow of participants through the study. AHT=Antihypertensive.

Figure 2. Each 5-day gap in antihypertensive medication adherence was associated with an 18% increased risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). Wider confidence intervals were observed at the upper end of the graph due to the low number of participants with 6 or more 5-day gaps in antihypertensive refill behaviour.

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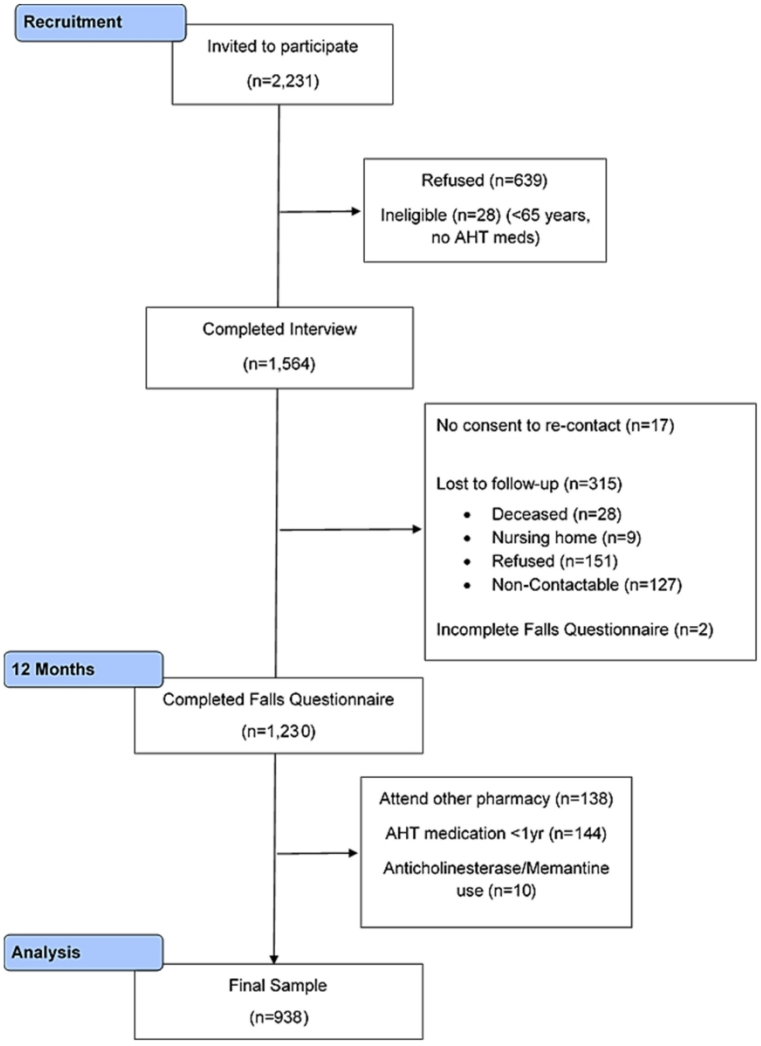

Figure 1. Flow of participants through the study. AHT=Antihypertensive.

190x275mm (300 x 300 DPI)

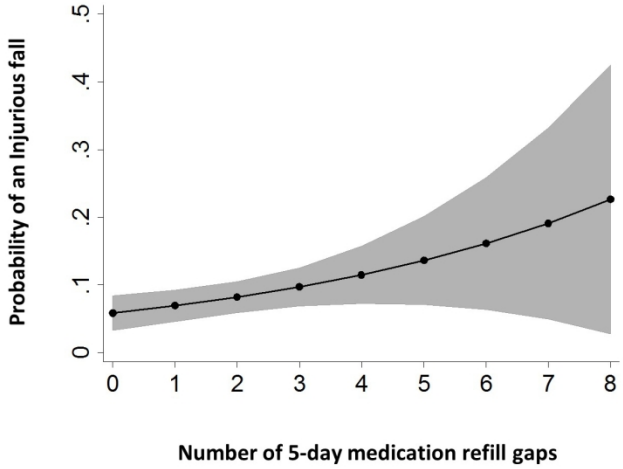

Figure 2. Each 5-day gap in antihypertensive medication adherence was associated with an 18% increased risk of an injurious fall during follow-up (aRR 1.18, 95% CI 1.02 – 1.37, p=0.024). Wider confidence intervals were observed at the upper end of the graph due to the low number of participants with 6 or more 5-day gaps in antihypertensive refill behaviour.

149x199mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 14
		(*e*) Describe any sensitivity analyses	Page 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10
		(b) Give reasons for non-participation at each stage	Page 6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	Page 4
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Table 2

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 & 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.