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Association between bisphosphonate therapy and outcomes from rehabilitation in older people

Abstract

Background

Bisphosphonate therapy may have actions beyond bone, including effects on cardiovascular, immune and muscle function. We tested whether bisphosphonate treatment is associated with improved outcomes in older people undergoing inpatient rehabilitation

Methods

Analysis of prospectively collected, linked routine clinical datasets. Participants were divided into never users of bisphosphonates, use prior to rehabilitation only, use after rehabilitation only, and current users (use before and after rehabilitation). We calculated change in 20-point Barthel scores during rehabilitation, adjusting for comorbid disease and laboratory data using multivariable regression analysis. Cox regression analyses were performed to analyse the association between bisphosphonate use and time to death or hospitalisation.

Results

2797 patients were included in the analysis. Current bisphosphonate users showed greater improvement in Barthel score during rehabilitation than non-users (5.0 points [95%CI 4.3 to 5.7] vs 3.8 [95%CI 3.6 to 3.9]), but no difference compared to those receiving bisphosphonates only after discharge (5.1 [95%CI 4.6 to 5.5]). Previous bisphosphonate use was significantly associated with time to death (adjusted hazard ratio 1.41 [95%CI 1.15 to 1.73]) but less strongly with time to combined endpoint of hospitalisation or death (adjusted hazard ratio 1.18 [95%CI 0.98 to 1.48]). Use after discharge from rehabilitation was associated with reduced risk of death

(adjusted hazard ratio 0.64 [95%CI 0.55 to 0.73]; hazard ratio per year of bisphosphonate prescription 0.98 [95%CI 0.97 to 0.99])

Conclusion

Bisphosphonate use is unlikely to be causally associated with improved physical function in older people, but continuing use may be associated with lower risk of death.

Keywords: Older, Bisphosphonate, rehabilitation, resilience

Introduction

Bisphosphonates are widely used as antiresorptive agents for treating osteoporosis. They bind to bone with high affinity, impairing the ability of osteoclasts to adhere to and resorb bone; they also promote apoptosis of osteoclasts, impair maturation of osteoclast progenitors, and hence reduce bone turnover and resorption. The consequent increase in bone mineral density reduces the relative risk of post-menopausal osteoporotic fractures by between 30 and 70%[1]. In addition, bisphosphonate therapy may have effects beyond reducing fracture rates; in a recent meta-analysis, bisphosphonate therapy reduced all-cause mortality by 10% in high-risk groups, an effect that appears much greater than can be attributed solely to their effect on fracture reduction[2,3]. Furthermore, the reduction in all-cause mortality is not driven by reductions in specific major event groups (e.g. cardiovascular events, cancer or infection) but appears to be distributed across multiple causes of death[4].

Bisphosphonates have been shown to display a number of pleiotropic biological effects that might contribute to the above findings. First, nitrogen-containing bisphosphonates may exhibit actions on lipid metabolism similar to statin medications, via inhibition of the mevalonate pathway, thereby reducing the progression of atherogenic processes[5-8]. Statins themselves have been associated with improved outcomes from rehabilitation[9,10]. Related effects on the mevalonate pathway underlie alterations to lipid anchoring of a number of intracellular signalling molecules, which may explain the anticancer effects of bisphosphonates therapy observed in some studies. Effects on reducing oxidative stress have also been postulated; oxidative stress in turn has been linked to a wide range of disease states including cardiovascular disease[11], cancer, and sarcopenia - the age-related loss of muscle mass and

strength[12,13]. Bisphosphonates may also initially promote low-grade, chronic inflammation (via production of pro-inflammatory cytokines[14,15]) which in turn may activate protective mechanisms at a cellular level which protect against the consequences of more severe inflammation. Finally, recent preclinical data suggests that zoledronate can protect mesenchymal stem cells against the accumulation of DNA damage[16].

Rehabilitation is an essential step on the pathway back to independent function for older people who have suffered intercurrent illness. Whilst it is recognised that rehabilitation is dependent on a number of factors, not least the quality and input of an exercise programme, it can be interrupted by further intercurrent illness with a consequent vicious cycle of immobility, worsening physical function and increased susceptibility to illness. Rehabilitation may also progress slowly due to intrinsic pathophysiological limitations like sarcopenia. Successful rehabilitation in older people might thus be enhanced by agents with pleiotropic effects on a variety of biological pathways to improve resilience; agents that improve muscle function directly would clearly be useful, but agents that either reduce intercurrent illness or mitigate the effects of intercurrent illness may also be of benefit. We therefore tested whether bisphosphonate treatment was associated with improved outcomes in a large cohort of older people undergoing inpatient rehabilitation, using routinely collected health and functional data.

Methods

Data Sources and Patient Population

This study was performed as part of a data linkage project which combined detailed healthcare data held on residents of Tayside, Scotland, held by the University of Dundee Health Informatics Centre (HIC) with functional outcome data on older people who had undergone inpatient rehabilitation within the Dundee Medicine for the Elderly service (DOME). Data

linkage was achieved using the Community Health Index (CHI), a unique healthcare identifier assigned to all Scottish healthcare users. Data linkage was carried out by HIC, with the combined, anonymised dataset hosted in a safe haven facility, which allows analysis by permitted parties without release of raw data outside the safe haven facility.

The DOME functional outcome data forming the basis of this analysis has been described previously[17,18]. We used an extended version of this dataset, which was collected prospectively on all patients admitted for rehabilitation over a 13 year period between 1st January 1999 and 31st December 2011, and comprised approximately 5500 admissions on 4382 individuals. The HIC database is a comprehensive set of health data on 400,000 people within the Tayside, Scotland area. In this study, health data was extracted from the HIC database for those patients registered on the DOME database. Prescribing information, biochemistry and haematology results, hospitalization data and diagnoses (Scottish Morbidity Register 01) coded using ICD-10 codes were available. Data on date of death was obtained via the Scottish Government Records Office, which records all deaths registered in Scotland. For this analysis, the cohort consisted of patients undergoing their first admission to the rehabilitation service, and omitted repeat admissions to the rehabilitation service, so that effects of previous rehabilitation did not impact on either baseline function or response to rehabilitation.

Bisphosphonate use

Bisphosphonate use was defined by extracting prescription records for bisphosphonate medications contained in the British National Formulary. All bisphosphonates used in the study population were included, namely alendronate, risedronate, etidronate, clodronate and ibandronate. Zoledronic acid was not used within the service covered by this cohort during the time period under study. Data on prescribing are held only for prescriptions dispensed in the

community, not in hospital; no electronic record exists for in-hospital prescriptions. We thus used community prescribing data from before and after each inpatient rehabilitation period to categorise patients into four groups: Current users comprised patients who were prescribed bisphosphonates at any time during the six months immediately prior and at any time in the 6 months subsequent to rehabilitation. Previous users comprised patients prescribed bisphosphonates in the two year period prior to rehabilitation, excluding those in group A. Subsequent users comprised patients who received bisphosphonates only after discharge from rehabilitation, and did not receive bisphosphonates in the two years prior to admission. Never users consisted of patients with no prescription for bisphosphonates recorded either before or after the rehabilitation stay at any point covered by the database (dating back to 01/01/1998 and censored at 04/05/2012). This approach allowed us to dissect out whether changes associated with bisphosphonate use were likely to be due to bisphosphonates, or due to unmeasured characteristics of patients who were more likely to be prescribed bisphosphonates. Relatively wide time windows were employed in part due to the known long duration of action of bisphosphonate medications, and because prescriptions for bisphosphonates are renewed infrequently due to the weekly dosing of many preparations.

Measurement of functional status

The functional outcome utilised in this study was the 20 point Barthel Index[19], a widely used and validated measure of patients' abilities in activities of daily living. The Barthel index consists of 10 separate function categories each with possible scores of 0/1, 0/1/2, or 0/1/2/3, yielding a total score out of 20, with a higher score indicating greater independence. A Barthel score was recorded by rehabilitation staff at admission and at discharge from inpatient

rehabilitation. Discharge destination (coded as return to own home or elsewhere) was obtained from the rehabilitation dataset.

Comorbidities and other covariates

Covariates were selected on the basis of clinical plausibility and prior knowledge, based on their likelihood to interact with bisphosphonate therapy, affect rehabilitation outcome, physical function or susceptibility to illness. Age and sex were obtained from healthcare demographic information held within HIC data. Previous hospitalisation for myocardial infarction, stroke, COPD and heart failure were coded from ICD-10 codes held in HIC healthcare data. Previous diagnoses of cancer were obtained from SMR06 (Scottish Cancer Registry) data, and previous diagnoses of diabetes mellitus were obtained from the Scottish Care Information - Diabetes Collaboration (SCI-DC) database, which records all diagnoses of diabetes within Scotland. Renal function (recorded as estimated glomerular filtration rate [eGFR] and calculated by the Modified Diet in Renal Disease [MRDR4] equation[20], serum calcium and serum albumin values were extracted from routinely collected biochemistry data held in HIC; the value closest to the date of admission to rehabilitation was used. Prescribed calcium and vitamin D supplementation was assessed by extraction of prescribing data in a similar way to bisphosphonate medication.

Data Analysis

Data analyses were performed using SPSS v21 (IBM, New York, USA) or SAS v9.2 (SAS Institute Inc., Cary, NC, USA). Patients who died during admission or had a missing admission or discharge Barthel score were excluded from analysis. Where patients had had multiple admissions to the rehabilitation service, only the first admission was included in the analysis, and subsequent admissions were ignored. Baseline factors were compared by bisphosphonate

use, using one-way ANOVA for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, and Pearson's Chi-squared test for categorical variables. The association between bisphosphonate use and improvement in Barthel score during rehabilitation was assessed by multivariable regression analysis, adjusting for age, sex, admission Barthel score, calcium/vitamin D use, renal function (eGFR), albumin, corrected calcium, previous diagnosis of diabetes mellitus, previous indication of IHD, stroke, cancer, COPD and CHF, and number of prescribed medications. A sensitivity analysis was conducted excluding those patients who had received non-aminobisphosphonates (clodronate or etidronate) due to their lack of effect on the mevalonate pathway. Because calcium and vitamin D are almost always co-administered with bisphosphonates, we analysed whether calcium and vitamin D use was associated with differences in rehabilitation outcomes, death or time to hospitalisation in the group of patients who had never taken bisphosphonates; if a significant effect were to be evident, the results of analyses of bisphosphonate exposure would not be reliably attributable to bisphosphonates. For those taking bisphosphonates prior to rehabilitation, the number of days of exposure in the year prior to rehabilitation was calculated – those on weekly preparations counted as 7 days per exposure, those on monthly preparations counted as 30 days per exposure. Adherence, which is known to be suboptimal with oral bisphosphonates, could not be directly calculated as data on encashed prescriptions was available, but date of decision to commence prescribing was not.

We conducted Cox regression analyses to estimate the association between bisphosphonate use and time to death after discharge from rehabilitation; similar analyses were conducted for time to a combined endpoint of death or next hospitalisation. For each analysis, models were run both unadjusted and adjusted for the variables listed above including discharge destination. Models were run comparing each of the groups against those patients never using

bisphosphonates. To separate out the effect of previous exposure to bisphosphonates (which might be a marker for unmeasured frailty or comorbidity) from the effect of subsequent use, a separate analysis was run using any use prior to rehabilitation as a distinct variable from any use after discharge from rehabilitation. Further analyses were run using time-dependent Cox regression analyses; the cumulative exposure to bisphosphonates post-discharge was included as a time-dependent variable, with pre-admission exposure included as a categorical variable and other adjusting variables included as listed above.

Results

Data were available on 4382 first admissions to rehabilitation. 95 patients were omitted from the analysis because they had last received bisphosphonates greater than 2 years prior to admission. 366 patients died during their rehabilitation stay (27/392 [6.9%] of previous bisphosphonate users versus 339/3895 (8.7%) of never users, p=0.22). Of the remainder of the cohort, 1124 patients were excluded due to missing admission or discharge Barthel data. Analyses were therefore conducted on the remaining 2797 patients. Table 1 gives the baseline details for the four analysis groups.

No effect of calcium and vitamin D supplementation was evident on either rehabilitation outcomes (3.8 points vs 3.7 points improvement during rehabilitation, p=0.15), risk of death (hazard ratio 0.90, 95%CI 0.72 to 1.12), or risk of hospitalisation or death (hazard ratio 0.99, 95%CI 0.81 to 1.21) in the group of patients who had never used bisphosphonates. Calcium and vitamin D use was included as a covariate in all subsequent analyses. Table 2 shows the association between different patterns of bisphosphonate exposure and improvements seen in Barthel score during inpatient rehabilitation, giving both unadjusted results and results adjusted for the variables listed above. Excluding those patients who had used non-nitrogen-containing bisphosphonates (clodronate or etidronate) did not significantly change the results (adjusted improvement in Barthel scores for never, previous, current and subsequent users: 3.8 [3.6 to 3.9]; 3.7 [2.9 to 4.5]; 5.8 [4.9 to 6.6]; 5.1 [4.6 to 5.5]; p=0.17 for current vs subsequent users). Exposure to bisphosphonates in the year prior to rehabilitation varied, with 43% of those taking bisphosphonates prior to rehabilitation taking less than 180 days equivalent in the year prior to admission. However there was no significant correlation between the number of days of

bisphosphonate use in the year prior to rehabilitation and the improvement in Barthel score (unadjusted r=-0.05, p=0.49; adjusted r=-0.12, p=0.15)

Table 3 gives the results of both unadjusted and adjusted Cox regression analyses, showing the effect of exposure to bisphosphonates post-discharge on both survival and time to the combined death or next hospitalisation endpoint. Time-dependent Cox regression analyses showed similar results; the adjusted hazard ratio for death post-discharge was 0.98 (95%CI 0.97 to 0.99) per year of post-discharge bisphosphonate exposure, and the adjusted hazard ratio for death or next hospitalisation post-discharge was 1.01 (95%CI 0.98 to 1.04) per year of post-discharge bisphosphonate exposure.

Discussion

The results from this analysis do not support a beneficial effect of bisphosphonate use on physical function outcomes in rehabilitation, as measured by the Barthel score. Although current bisphosphonate users achieved greater improvement in function during rehabilitation compared to previous users and never users, current users showed similar improvements to those who used bisphosphonates only after discharge from rehabilitation. For this latter group, drug exposure occurred only after discharge from rehabilitation and thus their functional improvement cannot be attributed to the effects of bisphosphonates. Our results do not therefore support a causal association between bisphosphonate therapy and functional improvement in this cohort. For post-discharge time to death and to next hospitalisation, our results suggest that previous exposure to bisphosphonates is a marker of increased risk of death or hospitalisation, but that ongoing exposure to bisphosphonates is associated with reduced hazard of death, and a less significant reduction in hazard of hospitalisation.

To our knowledge, this is the first study to examine the relationship between bisphosphonate use and functional outcomes during rehabilitation. The results of our analyses do not suggest a biological effect of bisphosphonates on biological pathways that might improve performance during rehabilitation – either via direct effects on musculoskeletal function or by reducing adverse events that interrupt rehabilitation. Rather, the results are consistent with current and future bisphosphonate use being a marker for unmeasured patient characteristics that are associated with better rehabilitation outcomes. Fitter, more robust patients who are perceived as having more to gain and longer to live may be more likely to be given bisphosphonates, and although the Barthel scores at admission to rehabilitation were similar across all four groups, there are other aspects of physical function and frailty that we were unable to measure directly using this routinely collected dataset.

A further potential confounder to address in this context is the frequent co-administration of calcium and vitamin D in routine treatment with bisphosphonates. UK clinical guidelines state that clinicians should ensure patients have an adequate intake of calcium and are vitamin D replete before prescribing bisphosphonates. The majority of older, frail patients in Scotland have low 25-hydroxyvitamin D levels – and our cohort are even more likely to have low levels given their prolonged stay in hospital. In the absence of vitamin D repletion, the increases in bone mineral density and anti-fracture efficacy associated with bisphosphonates, are attenuated[21]. Vitamin D has a direct effect on muscle function[22], and therefore supplementation with this agent could confound the association between bisphosphonates and functional outcomes. We did not have data on 25-hydroxyvitamin D levels for this cohort, and thus we cannot completely adjust for the effect that vitamin D repletion might have had on the analyses. However, analysis of the large group of patients who had never received a bisphosphonate did

not support an effect of calcium and vitamin D on either rehabilitation outcomes, survival or hospitalisation in this group, making this explanation less likely.

The results from analysis of time to death are broadly consistent with other randomised trial and observational data[3,4,23,24] suggesting that bisphosphonates are associated with a lower risk of death. This is despite the fact that previous bisphosphonate use appears to be a risk marker for higher rates of death and hospitalisation. Such a finding, whilst paradoxical at first sight, is consistent with the fact that bisphosphonates will typically be used in those with a disease (osteoporosis) with major adverse consequences on fitness and function, which is itself associated with other life-shortening disease complexes (particularly cardiovascular disease[5,25]). Thus being prescribed bisphosphonates at some previous time may be a marker of a group at increased risk of death, but greater exposure to bisphosphonates themselves could still confer protective effects. Less striking results were seen on analysing time to hospitalisation or death; some previous studies have suggested lower death rates with bisphosphonate use, but not lower event rates for vascular disease. This would be consistent with our findings, and one possibility is that bisphosphonates might not reduce event rates, but might reduce the severity or impact of events on homeostatic function – i.e. they might enhance biological resilience[26] via yet to be determined mechanisms. It is noteworthy that the more potent bisphosphonates are known to induce an acute-phase inflammatory response in some users[2]; inflammatory responses are also thought to contribute to the pathophysiology underlying phenomena such as ischaemic preconditioning in different organ systems[27,28]. Another possible mechanism is via anti-apoptotic effects; although bisphosphonates promote apoptosis of osteoclasts, they inhibit apoptosis of osteoblasts and osteoclasts, possibly via effects on pathways linked to connexin 43 [29,30]. Similar pathways are present in other tissues,

including cardiomyocytes[31], although the actions of bisphosphonates on apoptosis in human organ systems outwith bone remain to be elucidated.

Our study had a number of significant strengths. The dataset combined detailed health and functional outcomes data on a large set of patients undergoing rehabilitation in the real world, which enhances the generalisability of the data. Use of prescribing data from both before and after rehabilitation allowed us to test causal relationships in a way that would not have been possible without post-discharge prescribing data; these data enabled a more robust schema to be used to determine bisphosphonate treatment level (including use up to two years prior to rehabilitation and subsequent use), as opposed to a simple dichotomous indicator of treatment or no treatment at admission. Furthermore, the prescribing data comprises prescriptions encashed by patients and dispensed by pharmacists, rather than merely prescriptions written by physicians, thus the prescribing data may better reflect medication adherence than measures based on analysing numbers of prescriptions written. Combining detailed biochemical data allowed us to adjust analyses for albumin and renal function, both of which are important potential confounders.

A number of weaknesses deserve comment. The use of routine data limits the type of measures of frailty and function to those available from clinical practice when the data were collected, and missing data are frequent. Adherence was not measured directly; although prescriptions were dispensed we have no measure of ingestion of medication. Furthermore, we cannot account for medications available without prescription, which included low-dose calcium and vitamin D. Although intravenous bisphosphonates such as ibandronate and zoledronate were not used within our service (which included osteoporosis management) during the time period studied, we cannot exclude the possibility that a few patients received courses of intravenous

bisphosphonates (e.g. to treat hypercalcaemia of malignancy) via oncology or other services; community prescribing data does not capture this use. We did not attempt to distinguish between different types of bisphosphonate; the majority of patients took once-weekly oral bisphosphonates. Although there may be different effects between different agents, the effects on mortality from trials appear to be broadly consistent in meta-analysis[3]. A further potential limitation is that we did not have access to 25-hydroxyvitamin D or PTH levels on patients; we are therefore unable to test whether vitamin D insufficiency or secondary hyperparathyroidism might modify the results of our analysis.

Bisphosphonates have a long duration of action on bone[32], in part because they bind to hydroxyapatite crystals. The time course of biological effects in other organ systems is less clear[33]; our analysis assumes an extended duration of action after dosing, but this may not be the case for all potential biological effects. Similarly, the effects of bisphosphonates in this analysis are difficult to fully separate from any effects of calcium and vitamin D, both of which are known to have pleiotropic biological effects across multiple organ systems[22]. Finally, the cohort that we used comprised older patients selected for inpatient rehabilitation, and the cohort was exclusively white and mostly Northern European in ancestry. The findings from this cohort are not therefore necessarily generalizable to cohort comprising younger, fitter patients, unselected older patients or patients with different racial or ethnic background.

Our work suggests a number of avenues for future research. Replication of these findings in other cohorts would be of interest to ensure that an effect has not been missed by our analysis. Although the lack of evidence for a causal relationship between bisphosphonate use and improved rehabilitation outcomes does not support conducting trials in this specific area, the idea that bisphosphonates might be able to reduce death rates in older people by mitigating the

deleterious impact of health events is an intriguing one, which merits further study. Studies designed specifically to examine this idea are needed, and should not be confined to patients with osteoporosis; both studies to explore possible biological mechanisms for the lower mortality seen in bisphosphonate users, and studies to test whether such an effect can be reproduced in those without osteoporosis, would be of considerable interest.

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438 **Table 1. Baseline Details (n=2797)**

439

	Never used	Previous use	Current use	Subsequent use
N (%)	2351 (84)	124 (4)	95 (3)	227 (8)
Mean age (SD)	84.2 (7.6)	83.3 (6.9)	84.7 (6.3)	83.7 (7)
Male sex (%)	1056 (45)	24 (19)	15 (16)	58 (26)
Median length of stay (IQR)	36 (46)	33 (44)	35 (46)	38 (40)
Previous myocardial infarction (%)	533 (23)	38 (31)	33 (35)	41 (18)
Previous stroke (%)	533 (23)	17 (14)	17 (18)	41 (18)
Previous heart failure (%)	370 (16)	22 (18)	14 (15)	14 (6)
Previous hip fracture (%)	188 (8)	10 (8)	11 (12)	47 (21)
Previous COPD (%)	299 (13)	33 (27)	20 (21)	27 (12)

Previous diagnosis of cancer (%)	290 (12)	18 (15)	7 (7)	25 (11)
Diabetes mellitus (%)	418 (18)	20 (16)	11 (12)	37 (16)
Mean admission Barthel score (SD)	10.4 (3.9)	10.9 (3.4)	10.5 (3)	10.9 (3.2)
Median no of medications at admission (IQR)	2 (5)	3 (6)	7 (4)	2 (3)
Discharged to own home (%)	1743 (74)	97 (78)	87 (92)	202 (89)
Mean adjusted serum calcium (mmol/L) (SD)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)
Mean eGFR (ml/min) (SD)	61.2 (23.7)	68 (31.5)	64.5 (28.2)	65.2 (23.2)
Mean haemoglobin (g/dL) (SD)	12.1 (1.9)	11.7 (1.8)	11.9 (2.2)	11.8 (1.8)
Mean albumin (g/L) (SD)	36.7 (4.9)	36.0 (4.6)	37.5 (4.5)	36.9 (4.9)

Table 2. Association between Bisphosphonate use and change in Barthel Score during Rehabilitation

	Never used	Previous use	Current use	Subsequent use
Unadjusted change in Barthel score (95% CI)	3.8 (3.6-3.9)	3.4 (2.8-4.0)	5.2** (4.6-5.9)	5.0** (4.6-5.5)
Adjusted change in Barthel score (95% CI)	3.8 (3.6-3.9)	3.4 (2.8-4.0)	5.0 ** (4.3-5.7)	5.1** (4.6-5.5)
Unadjusted length of stay (95% CI) (days)	57 (54.6-59)	46 (36-57)	51 (39-63)	54 (47-62)
Adjusted length of stay (95% CI) (days)	56 (54-58)	50 (40-59)	62 (50-73)	54 (47-61)

*P<.05, **P<.001 vs never users

Adjusted for: Baseline Barthel score, age, sex, comorbid disease (myocardial infarction, stroke, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, previous cancer), medication burden, recent hip fracture, baseline albumin, calcium, renal function (eGFR), and haemoglobin

Barthel score range 0 to 20; higher values indicate better function

Table 3. Cox Regression Analysis for Time to Death or next Hospitalisation

	Never used (n=2459)	Previous use (n=133)	Current use (n=100)	Subsequent use only (n=237)
Unadjusted hazard ratio for death (95% CI)	1	1.39 (1.13 to 1.69)	0.79 (0.62 to 1.00)	0.50 (0.43 to 0.60)
Adjusted hazard ratio for death (95% CI)	1	1.41 (1.15 to 1.73)	1.00 (0.77 to 1.29)	0.57 (0.48 to 0.67)
Unadjusted hazard ratio for next hospitalisation or death (95% CI)	1	1.21 (1.00 to 1.45)	1.20 (0.98 to 1.47)	0.81 (0.71 to 0.93)
Adjusted hazard ratio for next hospitalisation or death (95% CI)	1	1.18 (0.98 to 1.48)	1.27 (1.01 to 1.59)	0.88 (0.77 to 1.02)

	Previous use vs no previous use	Use post-discharge vs no use post-discharge
Unadjusted hazard ratio for death (95% CI)	1.13 (0.97 to 1.32)	0.56 (0.48 vs 0.65)
Adjusted hazard ratio for death (95% CI)	1.32 (1.11 to 1.56)	0.64 (0.55 to 0.73)
Unadjusted hazard ratio for next hospitalisation or death (95% CI)	1.23 (1.07 to 1.41)	0.89 (0.79 to 1.00)
Adjusted hazard ratio for next hospitalisation or death (95% CI)	1.24 (1.06 to 1.44)	0.95 (0.84 to 1.08)

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