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1 **Association between bisphosphonate therapy and**
2 **outcomes from rehabilitation in older people**

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27 **Association between bisphosphonate therapy and outcomes from**
28 **rehabilitation in older people**

29

30 **Abstract**

31 *Background*

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

35

36 *Methods*

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

43

44 *Results*

45 2797 patients were included in the analysis. Current bisphosphonate users showed greater
46 improvement in Barthel score during rehabilitation than non-users (5.0 points [95%CI 4.3 to
47 5.7] vs 3.8 [95%CI 3.6 to 3.9]), but no difference compared to those receiving
48 bisphosphonates only after discharge (5.1 [95%CI 4.6 to 5.5]). Previous bisphosphonate use
49 was significantly associated with time to death (adjusted hazard ratio 1.41 [95%CI 1.15 to
50 1.73]) but less strongly with time to combined endpoint of hospitalisation or death (adjusted
51 hazard ratio 1.18 [95%CI 0.98 to 1.48]). Use after discharge from rehabilitation was

52 associated with reduced risk of death (adjusted hazard ratio 0.64 [95%CI 0.55 to 0.73];
53 hazard ratio per year of bisphosphonate prescription 0.98 [95%CI 0.97 to 0.99])

54

55 *Conclusion*

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

58

59 Keywords: Older, Bisphosphonate, rehabilitation, resilience

60

61

62 **Introduction**

63

64 Bisphosphonates are widely used as antiresorptive agents for treating osteoporosis. They bind
65 to bone with high affinity, impairing the ability of osteoclasts to adhere to and resorb bone;
66 they also promote apoptosis of osteoclasts, impair maturation of osteoclast progenitors, and
67 hence reduce bone turnover and resorption. The consequent increase in bone mineral density
68 reduces the relative risk of post-menopausal osteoporotic fractures by between 30 and 70%¹.
69 In addition, bisphosphonate therapy may have effects beyond reducing fracture rates; in a
70 recent meta-analysis, bisphosphonate therapy reduced all-cause mortality by 10% in high-risk
71 groups, an effect that appears much greater than can be attributed solely to their effect on
72 fracture reduction^{2,3}. Furthermore, the reduction in all-cause mortality is not driven by
73 reductions in specific major event groups (e.g. cardiovascular events, cancer or infection) but
74 appears to be distributed across multiple causes of death⁴.

75

76 Bisphosphonates have been shown to display a number of pleiotropic biological effects that
77 might contribute to the above findings. First, nitrogen-containing bisphosphonates may
78 exhibit actions on lipid metabolism similar to statin medications, via inhibition of the
79 mevalonate pathway, thereby reducing the progression of atherogenic processes⁵⁻⁸. Statins
80 themselves have been associated with improved outcomes from rehabilitation^{9,10}. Related
81 effects on the mevalonate pathway underlie alterations to lipid anchoring of a number of
82 intracellular signalling molecules, which may explain the anticancer effects of
83 bisphosphonates therapy observed in some studies. Effects on reducing oxidative stress have
84 also been postulated; oxidative stress in turn has been linked to a wide range of disease states
85 including cardiovascular disease¹¹, cancer, and sarcopenia - the age-related loss of muscle

86 mass and strength^{12,13}. Bisphosphonates may also initially promote low-grade, chronic
87 inflammation (via production of pro-inflammatory cytokines^{14,15}) which in turn may activate
88 protective mechanisms at a cellular level which protect against the consequences of more
89 severe inflammation. Finally, recent preclinical data suggests that zoledronate can protect
90 mesenchymal stem cells against the accumulation of DNA damage¹⁶.

91

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

105

106 **Methods**

107 *Data Sources and Patient Population*

108 This study was performed as part of a data linkage project which combined detailed
109 healthcare data held on residents of Tayside, Scotland, held by the University of Dundee
110 Health Informatics Centre (HIC) with functional outcome data on older people who had

111 undergone inpatient rehabilitation within the Dundee Medicine for the Elderly service
112 (DOME). Data linkage was achieved using the Community Health Index (CHI), a unique
113 healthcare identifier assigned to all Scottish healthcare users. Data linkage was carried out by
114 HIC, with the combined, anonymised dataset hosted in a safe haven facility, which allows
115 analysis by permitted parties without release of raw data outside the safe haven facility.

116

117 The DOME functional outcome data forming the basis of this analysis has been described
118 previously^{17,18}. We used an extended version of this dataset, which was collected
119 prospectively on all patients admitted for rehabilitation over a 13 year period between 1st
120 January 1999 and 31st December 2011, and comprised approximately 5500 admissions on
121 4382 individuals. The HIC database is a comprehensive set of health data on 400,000 people
122 within the Tayside, Scotland area. In this study, health data was extracted from the HIC
123 database for those patients registered on the DOME database. Prescribing information,
124 biochemistry and haematology results, hospitalization data and diagnoses (Scottish Morbidity
125 Register 01) coded using ICD-10 codes were available. Data on date of death was obtained
126 via the Scottish Government Records Office, which records all deaths registered in Scotland.
127 For this analysis, the cohort consisted of patients undergoing their first admission to the
128 rehabilitation service, and omitted repeat admissions to the rehabilitation service, so that
129 effects of previous rehabilitation did not impact on either baseline function or response to
130 rehabilitation.

131

132 *Bisphosphonate use*

133 Bisphosphonate use was defined by extracting prescription records for bisphosphonate
134 medications contained in the British National Formulary. All bisphosphonates used in the
135 study population were included, namely alendronate, risedronate, etidronate, clodronate and

136 ibandronate. Zoledronic acid was not used within the service covered by this cohort during
137 the time period under study. Data on prescribing are held only for prescriptions dispensed in
138 the community, not in hospital; no electronic record exists for in-hospital prescriptions. We
139 thus used community prescribing data from before and after each inpatient rehabilitation
140 period to categorise patients into four groups: Current users comprised patients who were
141 prescribed bisphosphonates at any time during the six months immediately prior and at any
142 time in the 6 months subsequent to rehabilitation. Previous users comprised patients
143 prescribed bisphosphonates in the two year period prior to rehabilitation, excluding those in
144 group A. Subsequent users comprised patients who received bisphosphonates only after
145 discharge from rehabilitation, and did not receive bisphosphonates in the two years prior to
146 admission. Never users consisted of patients with no prescription for bisphosphonates
147 recorded either before or after the rehabilitation stay at any point covered by the database
148 (dating back to 01/01/1998 and censored at 04/05/2012). This approach allowed us to dissect
149 out whether changes associated with bisphosphonate use were likely to be due to
150 bisphosphonates, or due to unmeasured characteristics of patients who were more likely to be
151 prescribed bisphosphonates. Relatively wide time windows were employed in part due to the
152 known long duration of action of bisphosphonate medications, and because prescriptions for
153 bisphosphonates are renewed infrequently due to the weekly dosing of many preparations.

154

155

156 *Measurement of functional status*

157 The functional outcome utilised in this study was the 20 point Barthel Index¹⁹, a widely used
158 and validated measure of patients' abilities in activities of daily living. The Barthel index
159 consists of 10 separate function categories each with possible scores of 0/1, 0/1/2, or 0/1/2/3,
160 yielding a total score out of 20, with a higher score indicating greater independence. A

161 Barthel score was recorded by rehabilitation staff at admission and at discharge from
162 inpatient rehabilitation. Discharge destination (coded as return to own home or elsewhere)
163 was obtained from the rehabilitation dataset.

164

165 *Comorbidities and other covariates*

166 Covariates were selected on the basis of clinical plausibility and prior knowledge, based on
167 their likelihood to interact with bisphosphonate therapy, affect rehabilitation outcome,
168 physical function or susceptibility to illness. Age and sex were obtained from healthcare
169 demographic information held within HIC data. Previous hospitalisation for myocardial
170 infarction, stroke, COPD and heart failure were coded from ICD-10 codes held in HIC
171 healthcare data. Previous diagnoses of cancer were obtained from SMR06 (Scottish Cancer
172 Registry) data, and previous diagnoses of diabetes mellitus were obtained from the Scottish
173 Care Information - Diabetes Collaboration (SCI-DC) database, which records all diagnoses of
174 diabetes within Scotland. Renal function (recorded as estimated glomerular filtration rate
175 [eGFR] and calculated by the Modified Diet in Renal Disease [MRDR4] equation²⁰, serum
176 calcium and serum albumin values were extracted from routinely collected biochemistry data
177 held in HIC; the value closest to the date of admission to rehabilitation was used. Prescribed
178 calcium and vitamin D supplementation was assessed by extraction of prescribing data in a
179 similar way to bisphosphonate medication.

180

181 *Data Analysis*

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

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

207

208 We conducted Cox regression analyses to estimate the association between bisphosphonate
209 use and time to death after discharge from rehabilitation; similar analyses were conducted for
210 time to a combined endpoint of death or next hospitalisation. For each analysis, models were

211 run both unadjusted and adjusted for the variables listed above including discharge
212 destination. Models were run comparing each of the groups against those patients never using
213 bisphosphonates. To separate out the effect of previous exposure to bisphosphonates (which
214 might be a marker for unmeasured frailty or comorbidity) from the effect of subsequent use, a
215 separate analysis was run using any use prior to rehabilitation as a distinct variable from any
216 use after discharge from rehabilitation. Further analyses were run using time-dependent Cox
217 regression analyses; the cumulative exposure to bisphosphonates post-discharge was included
218 as a time-dependent variable, with pre-admission exposure included as a categorical variable
219 and other adjusting variables included as listed above.

220

221

222 **Results**

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

230

231 No effect of calcium and vitamin D supplementation was evident on either rehabilitation
232 outcomes (3.8 points vs 3.7 points improvement during rehabilitation, $p=0.15$), risk of death
233 (hazard ratio 0.90, 95%CI 0.72 to 1.12), or risk of hospitalisation or death (hazard ratio 0.99,
234 95%CI 0.81 to 1.21) in the group of patients who had never used bisphosphonates. Calcium
235 and vitamin D use was included as a covariate in all subsequent analyses. Table 2 shows the
236 association between different patterns of bisphosphonate exposure and improvements seen in
237 Barthel score during inpatient rehabilitation, giving both unadjusted results and results
238 adjusted for the variables listed above. Excluding those patients who had used non-nitrogen-
239 containing bisphosphonates (clodronate or etidronate) did not significantly change the results
240 (adjusted improvement in Barthel scores for never, previous, current and subsequent users:
241 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
242 subsequent users). Exposure to bisphosphonates in the year prior to rehabilitation varied, with
243 43% of those taking bisphosphonates prior to rehabilitation taking less than 180 days
244 equivalent in the year prior to admission. However there was no significant correlation

245 between the number of days of bisphosphonate use in the year prior to rehabilitation and the
246 improvement in Barthel score (unadjusted $r=-0.05$, $p=0.49$; adjusted $r=-0.12$, $p=0.15$)

247

248 Table 3 gives the results of both unadjusted and adjusted Cox regression analyses, showing
249 the effect of exposure to bisphosphonates post-discharge on both survival and time to the
250 combined death or next hospitalisation endpoint. Time-dependent Cox regression analyses
251 showed similar results; the adjusted hazard ratio for death post-discharge was 0.98 (95%CI
252 0.97 to 0.99) per year of post-discharge bisphosphonate exposure, and the adjusted hazard
253 ratio for death or next hospitalisation post-discharge was 1.01 (95%CI 0.98 to 1.04) per year
254 of post-discharge bisphosphonate exposure.

255

256

257 **Discussion**

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

270

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

283

284 A further potential confounder to address in this context is the frequent co-administration of
285 calcium and vitamin D in routine treatment with bisphosphonates. UK clinical guidelines
286 state that clinicians should ensure patients have an adequate intake of calcium and are vitamin
287 D replete before prescribing bisphosphonates. The majority of older, frail patients in Scotland
288 have low 25-hydroxyvitamin D levels – and patients in our cohort were even more likely to
289 have low levels given their prolonged stay in hospital. In the absence of vitamin D repletion,
290 the increases in bone mineral density and anti-fracture efficacy associated with
291 bisphosphonates, are attenuated²¹. Vitamin D has a direct effect on muscle function²², and
292 therefore supplementation with this agent could confound the association between
293 bisphosphonates and functional outcomes. We did not have data on 25-hydroxyvitamin D
294 levels for this cohort, and thus we cannot completely adjust for the effect that vitamin D

295 repletion might have had on the analyses. However, analysis of the large group of patients
296 who had never received a bisphosphonate did not support an effect of calcium and vitamin D
297 on rehabilitation outcomes, survival or hospitalisation in this group, making this explanation
298 less likely.

299

300 The results from analysis of time to death are broadly consistent with other randomised trial
301 and observational data^{3,4,23,24} suggesting that bisphosphonates are associated with a lower risk
302 of death. This is despite the fact that previous bisphosphonate use appears to be a risk marker
303 for higher rates of death and hospitalisation. Such a finding, whilst paradoxical at first sight,
304 is consistent with the fact that bisphosphonates will typically be used in those with a disease
305 (osteoporosis) with major adverse consequences on fitness and function, which is itself
306 associated with other life-shortening disease complexes (particularly cardiovascular
307 disease^{5,25}). Thus being prescribed bisphosphonates at some previous time may be a marker
308 of a group at increased risk of death, but greater exposure to bisphosphonates themselves
309 could still confer protective effects. Less striking results were seen on analysing time to
310 hospitalisation or death; some previous studies have suggested lower death rates with
311 bisphosphonate use, but not lower event rates for vascular disease. This would be consistent
312 with our findings, and one possibility is that bisphosphonates might not reduce event rates,
313 but might reduce the severity or impact of events on homeostatic function – i.e. they might
314 enhance biological resilience²⁶ via yet to be determined mechanisms. It is noteworthy that the
315 more potent bisphosphonates are known to induce an acute-phase inflammatory response in
316 some users²; inflammatory responses are also thought to contribute to the pathophysiology
317 underlying phenomena such as ischaemic preconditioning in different organ systems^{27,28}.
318 Another possible mechanism is via anti-apoptotic effects; although bisphosphonates promote
319 apoptosis of osteoclasts, they inhibit apoptosis of osteoblasts and osteoclasts, possibly via

320 effects on pathways linked to connexin 43^{29,30}. Similar pathways are present in other tissues,
321 including cardiomyocytes³¹, although the actions of bisphosphonates on apoptosis in human
322 organ systems outwith bone remain to be elucidated.

323

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

337

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

345 during the time period studied, we cannot exclude the possibility that a few patients received
346 courses of intravenous bisphosphonates (e.g. to treat hypercalcaemia of malignancy) via
347 oncology or other services; community prescribing data does not capture this use. We did not
348 attempt to distinguish between different types of bisphosphonate; the majority of patients
349 took once-weekly oral bisphosphonates. Although there may be different effects between
350 different agents, the effects on mortality from trials appear to be broadly consistent in meta-
351 analysis³. A further potential limitation is that we did not have access to 25-hydroxyvitamin
352 D or PTH levels on patients; we are therefore unable to test whether vitamin D insufficiency
353 or secondary hyperparathyroidism might modify the results of our analysis.

354

355 Bisphosphonates have a long duration of action on bone³², in part because they bind to
356 hydroxyapatite crystals. The time course of biological effects in other organ systems is less
357 clear³³; our analysis assumes an extended duration of action after dosing, but this may not be
358 the case for all potential biological effects. Similarly, the effects of bisphosphonates in this
359 analysis are difficult to fully separate from any effects of calcium and vitamin D, both of
360 which are known to have pleiotropic biological effects across multiple organ systems²².
361 Finally, the cohort that we used comprised older patients selected for inpatient rehabilitation,
362 and the cohort was exclusively white and mostly Northern European in ancestry. The findings
363 from this cohort are not therefore necessarily generalizable to cohort comprising younger,
364 fitter patients, unselected older patients or patients with different racial or ethnic background.

365

366 Our work suggests a number of avenues for future research. Replication of these findings in
367 other cohorts would be of interest to ensure that an effect has not been missed by our
368 analysis. Although the lack of evidence for a causal relationship between bisphosphonate use
369 and improved rehabilitation outcomes does not support conducting trials in this specific area,

370 the idea that bisphosphonates might be able to reduce death rates in older people by
371 mitigating the deleterious impact of health events is an intriguing one, which merits further
372 study. Studies designed specifically to examine this idea are needed, and should not be
373 confined to patients with osteoporosis; both studies to explore possible biological
374 mechanisms for the lower mortality seen in bisphosphonate users, and studies to test whether
375 such an effect can be reproduced in those without osteoporosis, would be of considerable
376 interest.

377

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382

383

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

472

	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)

473

474

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

476

	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)

477

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

479 Adjusted for: Baseline Barthel score, age, sex, comorbid disease (myocardial infarction, stroke, heart failure, chronic obstructive pulmonary disease, diabetes

480 mellitus, previous cancer), medication burden, recent hip fracture, baseline albumin, calcium, renal function (eGFR), and haemoglobin

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

482

483 **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)	

