

Appendix

The impact of preadmission oral bisphosphonate use on 30-day mortality following stroke: a population-based cohort study of 100,043 patients

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Table S1. ICD and ATC codes

Stroke	
AIS	ICD-8: 433-434; ICD-10: I63
ICH	ICD-8: 431; ICD-10: I61
SAH	ICD-8: 430; ICD-10: I60
Unspecified strokes	ICD-10: I64
CT scan	ICD-10: UXCA
MRI scan	ICD-10: UXMA
Bisphosphonates	ATC: M05BA01, M05BA04, M05BA06, M05BA07, M05BB01, M05BB03
Comedications	
Cardiovascular drugs	
Beta-blockers	ATC: C07
Calcium channel blockers	ATC: C08
Diuretics	ATC: C03
Nitrates	ATC: C01DA
Statins	ATC: C10AA, C10B, B04AB
Acetylsalicylic acid	ATC: B01AC06, N02BA01
Clopidogrel	ATC: B01AC04
Vitamin K antagonists	ATC: B01AA03, B01AA04
ACE-I, ARB	ATC: C09A-D
Other drugs	
Hormone replacement therapy	ATC: G03C, G03F, G03HB01
Systemic glucocorticoids	ATC: H02AB
SSRIs	ATC: N06AB
NSAIDs	ATC: M01A
Individual comorbidities	
Recent osteoporotic fracture	ICD-10: DM80 DS22.0-22.1, DS32.0, DS32.7A, DS32.8A, DS48.4, DS48.5, DS52.5-52.6, DS72.0-72.2, DS72.9
Non-recent fracture	ICD-8: 723.90, 805.10-805.11, 805.19, 805.21-805.22, 805.31-805.32, 813.20-813.21, 813.28-813.29, 813.47, 813.49, 813.57, 813.59, 813.99, 820.01-820.02, 820.08-820.12, 820.18-820.19; ICD-10: DM80 DS22.0-22.1, DS32.0, DS32.7A, DS32.8A, DS48.4, DS48.5, DS52.5-52.6, DS72.0-72.2, DS72.9
Simple osteoporosis	ICD-8: 723.09; ICD-10: DM81-82
Cardiovascular diseases	
Myocardial infarction	ICD-8: 410; ICD-10: I21, I22, I23
Angina pectoris	ICD-8: 413; ICD-10: I20.9, I25.1, I25.9
Atrial fibrillation or flutter	ICD-8: 427.93, 427.94; ICD-10: I48
Heart valve disease	ICD-8: 394-398; ICD-10: I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22
Intermittent arterial claudication	ICD-8: 443.89-443.99; ICD-10: I73.9
Venous thromboembolism	ICD-8: 451.00; ICD-10: I80.1-3, I26
Hypertension	ICD-8: 400-404; ICD-10: I10-I15
Other diseases	

Obesity	ICD-8: 277; ICD-10: E65-E68
Diabetes	ICD-8: 249-250; ICD-10: E10-E14, O24 (except O24.4), H36.0; ATC: A10B, A10A
Chronic kidney disease	ICD-8: 249.02, 250.02, 753.10-753.19, 582, 583, 584, 590.09, 593.20, 792; ICD-10: E10.2, E11.2, E14.2, N03, N05, N11.0, N14, N16, N18-N19, N26.9, Q61.1-Q61.4
COPD	ICD-8: 491-492; ICD-10: J41-44; ATC: R03
Alcoholism-related diseases	ICD-8: 291, 303, 456, 571.09, 571.10, 577.10; ICD-10: F10.1-9, G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1; ATC: N07BB
Cancer	ICD-8: 140-207; ICD-10: C00-C96
Dementia	ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30

Abbreviations: AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SSRIs, selective serotonin reuptake inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.

Table S2. Number of bisphosphonate users by drug type

	Stroke overall	AIS	ICH	SAH	Unspecified stroke
	N (%)	N (%)	N (%)	N (%)	N (%)
Current use^a					
All	3427 (100)	1730 (100)	444 (100)	112 (100)	1141 (100)
Alendronate	2821(82.3)	1430 (82.7)	365 (82.2)	95 (84.8)	931 (81.6)
Etidronate	352 (10.3)	159 (9.2)	47 (10.6)	8 (7.1)	138 (12.1)
Risedronate	67 (2.0)	37 (2.1)	8 (1.8)	4 (3.6)	18 (1.6)
Ibandronate	197 (5.7)	110 (6.4)	25 (5.6)	5 (4.5)	57 (5.0)
Recent use^b					
All	652 (100)	322 (100)	72 (100)	22 (100)	236 (100)
Alendronate	469 (71.9)	238 (73.9)	61 (84.7)	14 (63.6)	156 (66.1)
Etidronate	156 (23.9)	72 (22.4)	11 (15.3)	6 (27.3)	67 (28.4)
Risedronate	9 (1.4)	7 (2.2)	-	-	2 (1.3)
Ibandronate	49 (7.5)	23 (7.1)	4 (5.6)	3 (13.6)	19 (12.2)
New use^c					
All	723 (100)	349 (100)	97 (100)	24 (100)	253 (100)
Alendronate	564 (78.0)	277 (79.4)	75 (77.3)	22 (91.7)	159 (62.8)
Etidronate	136 (18.8)	63 (22.7)	19 (19.6)	2 (8.3)	52 (20.6)
Risedronate	12 (1.7)	6 (1.7)	2 (2.1)	-	4 (1.6)
Ibandronate	44 (6.1)	21 (6.0)	6 (6.2)	-	17 (6.7)
Long-term use^d					
All	2704 (100)	1381 (100)	347 (100)	88 (100)	888 (100)
Alendronate	2257 (83.5)	1153 (83.5)	290 (83.6)	73 (83.0)	741 (83.4)
Etidronate	216 (8.0)	96 (7.0)	28 (8.1)	6 (6.8)	86 (9.7)
Risedronate	55 (2.0)	31 (2.2)	6 (1.7)	4 (4.5)	14 (1.6)
Ibandronate	153 (5.7)	89 (6.4)	19 (5.5)	5 (5.7)	40 (4.5)

Notes: The individual drug types do not add up to the total number due to drug type shifters.

^aPrescription redemption within 90 days before admission date.

^bPrescription redemption within 90-180 days before admission date.

^cPrescription redemption within 90 days before admission day and no additional prescriptions.

^dPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions before this period.

Abbreviations: AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI confidence interval.

Table S3. Preadmission use of etidronate and 30-day mortality risk and mortality rate ratios following stroke

	Mortality risk % (95% CI)	MRRs (95% CI) Unadjusted	MRRs (95% CI) Adjusted^a	Propensity matched (95% CI)
Stroke overall				
No use ^b	13.9 (13.7; 14.2)	1 (reference)	1 (reference)	1 (reference)
Current use ^c	21.0 (17.1; 25.7)	1.57 (1.25; 1.97)	1.06 (0.84; 1.34)	1.04 (0.82; 1.33)
Recent use ^d	23.1 (17.2; 30.5)	1.74 (1.25; 2.41)	1.16 (0.84; 1.61)	1.36 (0.93; 2.00)
New use ^e	27.2 (20.5; 35.5)	2.12 (1.53; 2.92)	1.40 (1.01; 1.93)	1.50 (1.03; 2.17)
Long-term use ^f	17.1 (12.7; 22.9)	1.25 (0.90; 1.72)	0.86 (0.62; 1.19)	0.88 (0.63; 1.23)
AIS				
No use	8.5 (8.2; 8.7)	1 (reference)	1 (reference)	1 (reference)
Current use	12.0 (7.8; 18.1)	1.45 (0.92; 2.27)	0.79 (0.50; 1.24)	0.90 (0.57; 1.45)
Recent use	15.3 (8.8; 25.9)	1.90 (1.05; 3.43)	1.11 (0.61; 2.01)	1.49 (0.76; 2.95)
New use	15.9 (8.9; 27.5)	1.98 (1.06; 3.67)	1.05 (0.56; 1.95)	1.27 (0.62; 2.61)
Long-term use	9.4 (5.0; 17.2)	1.12 (0.58; 2.14)	0.62 (0.32; 1.20)	0.82 (0.42; 1.61)
ICH				
No use	34.5 (33.7; 35.4)	1 (reference)	1 (reference)	1 (reference)
Current use	44.7 (31.9; 59.9)	1.40 (0.91; 2.15)	1.19 (0.77; 1.83)	1.04 (0.66; 1.63)
Recent use	45.5 (22.0; 77.2)	1.50 (0.63; 3.61)	1.06 (0.44; 2.56)	1.11 (0.37; 3.39)
New use	52.6 (32.7; 75.6)	1.83 (0.98; 3.40)	1.52 (0.81; 2.84)	1.82 (0.88; 3.76)
Long-term use	39.3 (24.0; 59.6)	1.15 (0.64; 2.08)	0.99 (0.55; 1.80)	0.84 (0.46; 1.53)
SAH				
No use	23.2 (22.0; 24.5)	1 (reference)	1 (reference)	1 (reference)
Current use	25.0 (6.9; 68.5)	1.09 (0.27; 4.36)	0.59 (0.15; 2.41)	0.83 (0.19; 3.56)
Recent use	50.0 (19.6; 88.9)	2.84 (0.91; 8.82)	1.59 (0.50; 5.02)	1.94 (0.40; 9.38)
New use	-	-	-	-
Long-term use	33.3 (9.6; 80.5)	1.53 (0.38; 6.12)	0.75 (0.18; 3.08)	1.15 (0.27; 4.82)
Unspecified stroke				
No use	14.0 (13.6; 14.4)	1 (reference)	1 (reference)	1 (reference)
Current use	23.2 (17.0; 31.2)	1.75 (1.23; 2.47)	1.20 (0.84; 1.71)	1.11 (0.77; 1.60)
Recent use	25.4 (16.6; 37.6)	1.89 (1.17; 3.04)	1.31 (0.81; 2.11)	1.49 (0.86; 2.59)
New use	32.7 (21.8; 47.2)	2.59 (1.61; 4.16)	1.76 (1.09; 2.84)	1.74 (1.00; 3.04)
Long-term use	17.4 (10.9; 27.3)	1.28 (0.77; 2.12)	0.88 (0.53; 1.47)	0.84 (0.49; 1.41)

Notes: ^aAdjusted for sex, age groups, recent osteoporotic fracture (≤ 6 months), non-recent osteoporotic fracture (> 6 months), simple osteoporosis (no fracture), myocardial infarction, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, obesity, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease (includes inhalation medications for chronic pulmonary obstructive disease), alcoholism-related diseases, dementia, cancer, and use of cardiovascular drugs (angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor blockers, beta-blockers, calcium channel blockers, diuretics, nitrates, statins, acetylsalicylic acid, clopidogrel, and vitamin K antagonists), hormone replacement therapy, systemic glucocorticoids, non-steroidal-anti-inflammatory drugs, and selective-serotonin-receptor inhibitors.

^bNo prescription redemption within 0-180 days before admission date.

^cPrescription redemption within 90 days before admission date.

^dPrescription redemption within 90-180 days before admission date.

^ePrescription redemption within 90 days before admission day and no additional prescriptions.

^fPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions before this period.

Abbreviations: MRRs, mortality rate ratios, PS-matched, propensity-score-matched, AIS, acute ischemic stroke, ICH, intracerebral hemorrhage, SAH, subarachnoid hemorrhage, CI, confidence interval.

Table S4. Preadmission use of alendronate and 30-day mortality risk and mortality rate ratios following stroke

	Mortality risk % (95% CI)	MRRs (95% CI) Unadjusted	MRRs (95% CI) Adjusted^a	Propensity matched (95% CI)
Stroke overall				
No use ^b	13.9 (13.7; 14.2)	1 (reference)	1 (reference)	1 (reference)
Current use ^c	19.0 (17.6; 20.5)	1.41 (1.29; 1.53)	0.95 (0.87; 1.04)	0.93 (0.83; 1.05)
Recent use ^d	18.8 (15.6; 22.7)	1.39 (1.13; 1.72)	0.93 (0.75; 1.15)	1.04 (0.79; 1.37)
New use ^e	19.0 (16.0; 22.5)	1.41 (1.17; 1.71)	0.96 (0.79; 1.17)	1.03 (0.80; 1.33)
Long-term use ^f	19.0 (17.5; 20.7)	1.41 (1.28; 1.55)	0.94 (0.85; 1.04)	0.99 (0.87; 1.13)
AIS				
No use	8.5 (8.2; 8.7)	1 (reference)	1 (reference)	1 (reference)
Current use	11.9 (10.3; 13.7)	1.43 (1.23; 1.67)	0.87 (0.74; 1.02)	0.90 (0.74; 1.10)
Recent use	13.5 (9.8; 18.6)	1.66 (1.17; 2.35)	1.06 (0.75; 1.50)	1.10 (0.69; 1.78)
New use	10.9 (7.8; 15.2)	1.30 (0.91; 1.87)	0.77 (0.54; 1.12)	0.95 (0.59; 1.52)
Long-term use	12.1 (10.4; 14.2)	1.46 (1.23; 1.73)	0.89 (0.75; 1.06)	1.08 (0.86; 1.36)
ICH				
No use	34.5 (33.7; 35.4)	1 (reference)	1 (reference)	1 (reference)
Current use	44.1 (39.2; 49.4)	1.41 (1.20; 1.65)	1.06 (0.89; 1.25)	1.04 (0.85; 1.29)
Recent use	43.0 (31.7; 56.4)	1.34 (0.91; 1.97)	1.05 (0.71; 1.55)	1.01 (0.60; 1.69)
New use	44.0 (33.7; 55.9)	1.38 (0.98; 1.94)	1.03 (0.72; 1.46)	1.26 (0.78; 2.04)
Long-term use	44.1 (38.6; 50.1)	1.41 (1.19; 1.69)	1.07 (0.88; 1.29)	1.03 (0.81; 1.30)
SAH				
No use	23.2 (22.0; 24.5)	1 (reference)	1 (reference)	1 (reference)
Current use	41.1 (32.0; 51.7)	1.85 (1.34; 2.54)	1.14 (0.80; 1.62)	1.47 (0.93; 2.34)
Recent use	28.6 (11.8; 59.4)	1.29 (0.48; 3.43)	0.82 (0.30; 2.22)	1.29 (0.36; 4.63)
New use	54.6 (35.7; 75.6)	2.66 (1.50; 4.69)	1.68 (0.93; 3.03)	1.85 (0.76; 4.48)
Long-term use	37.1 (27.1; 49.2)	1.62 (1.11; 2.38)	0.98 (0.64; 1.48)	1.24 (0.72; 2.11)
Unspecified stroke				
No use	14.0 (13.6; 14.4)	1 (reference)	1 (reference)	1 (reference)
Current use	17.8 (15.5; 20.5)	1.31 (1.12; 1.53)	0.88 (0.75; 1.04)	0.83 (0.68; 1.02)
Recent use	16.7 (11.7; 23.5)	1.20 (0.81; 1.76)	0.74 (0.50; 1.10)	0.90 (0.55; 1.46)
New use	16.8 (12.2; 23.0)	1.24 (0.87; 1.75)	0.92 (0.65; 1.31)	0.87 (0.56; 1.35)
Long-term use	18.1 (15.5; 21.1)	1.33 (1.12; 1.58)	0.87 (0.73; 1.04)	0.87 (0.70; 1.09)

Notes: ^aAdjusted for sex, age groups, recent osteoporotic fracture (≤ 6 months), non-recent osteoporotic fracture (> 6 months), simple osteoporosis (no fracture), myocardial infarction, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, obesity, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease (includes inhalation medications for chronic pulmonary obstructive disease), alcoholism-related diseases, dementia, cancer, and use of cardiovascular drugs (angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor blockers, beta-blockers, calcium channel blockers, diuretics, nitrates, statins, acetylsalicylic acid, clopidogrel, and vitamin K antagonists), hormone replacement therapy, systemic glucocorticoids, non-steroidal-anti-inflammatory drugs, and selective-serotonin-receptor inhibitors.

^bNo prescription redemption within 0-180 days before admission date.

^cPrescription redemption within 90 days before admission date.

^dPrescription redemption within 90-180 days before admission date.

^ePrescription redemption within 90 days before admission day and no additional prescriptions.

^fPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions before this period.

Abbreviations: MRRs, mortality rate ratios; PS-matched, propensity-score-matched; AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI, confidence interval.

Table S5. Preadmission use of risedronate and 30-day mortality risk and mortality rate ratios following stroke

	Mortality risk % (95% CI)	MRRs (95% CI) Unadjusted	MRRs (95% CI) Adjusted^a	Propensity matched (95% CI)
Stroke overall				
No use ^b	13.9 (13.7; 14.2)	1 (reference)	1 (reference)	1 (reference)
Current use ^c	16.4 (9.5; 27.7)	1.17 (0.65; 2.11)	0.89 (0.49; 1.61)	0.77 (0.43; 1.38)
Recent use ^d	22.2 (6.1; 63.5)	1.58 (0.40; 6.27)	1.15 (0.29; 4.59)	1.18(0.31; 4.52)
New use ^e	16.7 (4.5; 51.8)	1.17 (0.29; 4.63)	0.70 (0.17; 2.79)	0.45 (0.06; 3.21)
Long-term use ^f	16.4 (8.9; 29.1)	1.17 (0.61; 2.25)	0.95 (0.49; 1.83)	0.82 (0.43; 1.57)
AIS				
No use	8.5 (8.2; 8.7)	1 (reference)	1 (reference)	1 (reference)
Current use	13.5 (5.9; 29.5)	1.57 (0.66; 3.77)	0.93 (0.39; 2.25)	0.98 (0.42; 2.28)
Recent use	14.3 (2.1; 66.6)	1.73 (0.25;12.14)	1.26 (0.18; 8.96)	1.20 (0.16; 8.85)
New use	16.7 (2.5; 72.7)	1.90 (0.27;13.46)	0.50 (0.07; 3.60)	-
Long-term use	12.9 (5.1; 30.8)	1.50 (0.57; 4.00)	1.19 (0.44; 3.18)	1.11 (0.43; 2.87)
ICH				
No use	34.5 (33.7; 35.4)	1 (reference)	1(reference)	1 (reference)
Current use	12.5 (1.9; 61.3)	0.33 (0.05; 2.30)	0.25 (0.04; 1.78)	0.24 (0.03; 1.82)
Recent use	-	-	-	-
New use	-	-	-	-
Long-term use	16.7 (2.5; 72.7)	0.45 (0.06; 3.17)	0.32 (0.05; 2.29)	0.33 (0.04; 2.52)
SAH				
No use	23.2 (22.0; 24.5)	1 (reference)	1 (reference)	1 (reference)
Current use	25.0 (4.0; 87.2)	1.16 (0.16; 8.21)	1.07 (0.15; 7.86)	0.88 (0.10; 7.51)
Recent use	-	-	-	-
New use	-	-	-	-
Long-term use	25.00 (4.0; 87.2)	1.16 (0.16; 8.21)	1.07 (0.15; 7.86)	0.86 (0.11; 6.97)
Unspecified stroke				
No use	14.0 (13.6; 14.4)	1 (reference)	1 (reference)	1 (reference)
Current use	22.2 (9.0; 48.9)	1.66 (0.63; 4.41)	1.39 (0.52; 3.72)	1.05 (0.40; 2.74)
Recent use	50.0 (9.00; 99.4)	3.86 (0.55; 27.01)	2.24 (0.32; 15.77)	2.82 (0.55;14.53)
New use	25.0 (4.0; 87.2)	1.91 (0.27; 13.52)	2.08 (0.29; 14.84)	1.27 (0.18; 9.01)
Long-term use	21.4 (7.5; 52.8)	1.59 (0.51; 4.90)	1.25 (0.40; 3.89)	1.03 (0.34; 3.18)

Notes: ^aAdjusted for sex, age groups, recent osteoporotic fracture (≤ 6 months), non-recent osteoporotic fracture (> 6 months), simple osteoporosis (no fracture), myocardial infarction, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, obesity, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease (includes inhalation medications for chronic pulmonary obstructive disease), alcoholism-related diseases, dementia, cancer, and use of cardiovascular drugs (angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor blockers, beta-blockers, calcium channel blockers, diuretics, nitrates, statins, acetylsalicylic acid, clopidogrel, and vitamin K antagonists), hormone replacement therapy, systemic glucocorticoids, non-steroidal-anti-inflammatory drugs, and selective-serotonin-receptor inhibitors.

^bNo prescription redemption within 0-180 days before admission date.

^cPrescription redemption within 90 days before admission date.

^dPrescription redemption within 90-180 days before admission date.

^ePrescription redemption within 90 days before admission day and no additional prescriptions.

^fPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions before this period..

Abbreviations: MRRs, mortality rate ratios; PS-matched, propensity-score-matched; AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI, confidence interval.

Table S6. Preadmission use of ibandronate and 30-day mortality risk and mortality rate ratios following stroke

	Mortality risk % (95% CI)	MRRs (95% CI) Unadjusted	MRRs (95% CI) Adjusted^a	Propensity matched (95% CI)
Stroke overall				
No use ^b	13.9 (13.7; 14.2)	1 (reference)	1 (reference)	1 (reference)
Current use ^c	18.3 (13.6; 24.5)	1.36 (0.98; 1.88)	0.99 (0.71; 1.37)	0.90 (0.64; 1.26)
Recent use ^d	18.4 (10.0; 32.3)	1.34 (0.70; 2.57)	0.87 (0.45; 1.68)	1.13 (0.57; 2.22)
New use ^e	18.2 (9.5; 33.1)	1.32 (0.66; 2.63)	0.97 (0.48; 1.94)	0.88 (0.41; 1.87)
Long-term use ^f	18.4 (13.1; 25.5)	1.37 (0.94; 1.98)	0.99 (0.68; 1.44)	0.98 (0.66; 1.43)
AIS				
No use	8.45 (8.21; 8.69)	1 (reference)	1(reference)	1 (reference)
Current use	11.0 (6.4; 18.5)	1.33 (0.75; 2.34)	0.96 (0.54; 1.70)	0.83 (0.46; 1.50)
Recent use	21.7 (9.7; 44.6)	2.65 (1.10; 6.37)	1.35 (0.56; 3.26)	2.33 (0.93; 5.84)
New use	9.5 (2.5; 33.0)	1.17 (0.29; 4.63)	0.85 (0.21; 3.42)	0.44 (0.06; 3.27)
Long-term use	11.3 (6.3; 20.0)	1.37 (0.74; 2.55)	0.98 (0.53; 1.83)	1.01 (0.53; 1.94)
ICH				
No use	34.5 (33.7; 35.4)	1 (reference)	1(reference)	1 (reference)
Current use	36.0 (20.6; 57.8)	1.12 (0.58; 2.15)	0.88 (0.46; 1.70)	0.83 (0.41; 1.68)
Recent use	25.0 (4.0; 87.2)	0.65 (0.09; 4.62)	0.53 (0.07; 3.78)	0.47 (0.07; 3.18)
New use	16.7 (2.5; 72.7)	0.46 (0.07; 3.29)	0.47 (0.07; 3.37)	0.51 (0.06; 4.41)
Long-term use	42.1 (23.7; 66.8)	1.35 (0.67; 2.70)	0.98 (0.49; 1.98)	1.06 (0.51; 2.24)
SAH				
No use	23.2 (22.0; 24.5)	1 (reference)	1 (reference)	1 (reference)
Current use	60.0 (24.7; 94.8)	3.26 (1.05;10.12)	3.68 (1.14;11.85)	2.64 (0.84; 8.26)
Recent use	33.3 (5.5; 94.6)	1.82 (0.26;12.94)	2.30 (0.31;16.96)	1.81 (0.18;17.82)
New use	-	-	-	-
Long-term use	60.0 (24.7; 94.8)	3.26 (1.05;10.12)	3.68 (1.14;11.85)	2.47 (0.83; 7.35)
Unspecified stroke				
No use	14.0 (13.6; 14.4)	1 (reference)	1(reference)	1 (reference)
Current use	21.1 (12.6; 34.1)	1.55 (0.88; 2.73)	1.03 (0.58; 1.81)	0.98 (0.56; 1.73)
Recent use	10.5 (2.7; 35.9)	0.76 (0.19; 3.06)	0.53 (0.13; 2.12)	0.59 (0.14; 2.58)
New use	29.4 (13.4; 56.9)	2.17 (0.90; 5.20)	1.50 (0.62; 3.62)	1.47 (0.61; 3.51)
Long-term use	17.5 (8.8; 33.2)	1.28 (0.61; 2.69)	0.84 (0.40; 1.76)	0.84 (0.39; 1.79)

Notes: ^aAdjusted for sex, age groups, recent osteoporotic fracture (≤ 6 months), non-recent osteoporotic fracture (> 6 months), simple osteoporosis (no fracture), myocardial infarction, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, obesity, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease (includes inhalation medications for chronic pulmonary obstructive disease), alcoholism-related diseases, dementia, cancer, and use of cardiovascular drugs (angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor blockers, beta-blockers, calcium channel blockers, diuretics, nitrates, statins, acetylsalicylic acid, clopidogrel, and vitamin K antagonists), hormone replacement therapy, systemic glucocorticoids, non-steroidal-anti-inflammatory drugs, and selective-serotonin-receptor inhibitors.

^bNo prescription redemption within 0-180 days before admission date.

^cPrescription redemption within 90 days before admission date.

^dPrescription redemption within 90-180 days before admission date.

^ePrescription redemption within 90 days before admission day and no additional prescriptions.

^fPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions before this period.

Abbreviations: MRRs, mortality rate ratios; PS-matched, propensity-score-matched; AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI, confidence interval.

Table S7: Preadmission bisphosphonate use and 30-day mortality following stroke, by gender, age, atrial fibrillation and fracture history

	Mortality rate ratios (95% CI)				
	Stroke overall	AIS	ICH	SAH	Unspecified stroke
Male					
Current use ^a	0.87 (0.70; 1.09)	0.82 (0.55; 1.21)	1.03 (0.68; 1.57)	2.07 (0.95; 4.51)	0.75 (0.52; 1.10)
Recent use ^b	0.94 (0.60; 1.49)	0.42 (0.13; 1.32)	1.92 (0.90; 4.08)	-	1.08 (0.55; 2.11)
New use ^c	0.88 (0.55; 1.41)	0.91 (0.40; 2.04)	0.49 (0.16; 1.52)	4.30 (0.96;19.12)	0.98 (0.46; 2.08)
Long-term use ^d	0.87 (0.68; 1.10)	0.79 (0.51; 1.22)	1.23 (0.79; 1.91)	1.77 (0.74; 4.21)	0.70 (0.46; 1.08)
Female					
Current use	1.00 (0.91; 1.09)	0.88 (0.75; 1.04)	1.07 (0.91; 1.27)	1.06 (0.73; 1.55)	0.99 (0.85; 1.16)
Former use	1.02 (0.84; 1.23)	1.27 (0.94; 1.72)	0.92 (0.61; 1.38)	1.19 (0.55; 2.57)	0.87 (0.62; 1.21)
New use	1.11 (0.93; 1.32)	0.80 (0.56; 1.13)	1.21 (0.88; 1.67)	1.28 (0.66; 2.47)	1.29 (0.97; 1.73)
Long-term use	0.96 (0.87; 1.06)	0.90 (0.76; 1.08)	1.04 (0.86; 1.26)	0.98 (0.63; 1.53)	0.90 (0.75; 1.08)
Age < 60 years					
Current use	1.53 (0.93; 2.53)	0.69 (0.16; 2.93)	1.64 (0.77; 3.46)	0.92 (0.21; 3.99)	2.20 (0.73; 6.60)
Recent use	-	-	-	-	-
New use	1.48 (0.65; 3.38)	1.29 (0.17; 9.71)	0.52 (0.07; 3.77)	0.76 (0.10; 6.00)	2.83 (0.75;10.70)
Long-term use	1.55 (0.84; 2.87)	0.46 (0.06; 3.40)	2.58 (1.10; 6.05)	1.13 (0.15; 8.69)	1.37 (0.19;10.07)
Age 60 – 69 years					
Current use	1.01 (0.75; 1.34)	0.74 (0.38; 1.42)	1.22 (0.77; 1.92)	1.05 (0.47; 2.35)	0.78 (0.42; 1.44)
Former use	1.49 (0.89; 2.49)	1.39 (0.50; 3.87)	0.90 (0.29; 2.83)	0.95 (0.11; 8.04)	2.10 (0.94; 4.69)
New use	0.72 (0.37; 1.40)	1.43 (0.45; 4.52)	0.47 (0.15; 1.49)	-	0.68 (0.21; 2.21)
Long-term use	1.08 (0.79; 1.48)	0.62 (0.29; 1.35)	1.55 (0.96; 2.52)	1.32 (0.57; 3.06)	0.78 (0.39; 1.57)
Age 70-79 years					
Current use	0.98 (0.84; 1.16)	0.89 (0.64; 1.23)	0.88 (0.66; 1.18)	1.07 (0.58; 1.99)	1.04 (0.78; 1.38)
Recent use	1.16 (0.82; 1.62)	1.49 (0.79; 2.83)	0.96 (0.52; 1.77)	1.97 (0.56; 6.88)	0.83 (0.45; 1.53)
New use	1.04 (0.76; 1.44)	0.65 (0.30; 1.38)	1.18 (0.67; 2.07)	2.32 (0.82; 6.56)	1.16 (0.69; 1.96)
Long-term use	0.97 (0.81; 1.17)	0.96 (0.67; 1.37)	0.83 (0.60; 1.16)	0.89 (0.43; 1.83)	0.99 (0.72; 1.37)
Age > 80 years					
Current use	0.96 (0.86; 1.07)	0.89 (0.75; 1.06)	1.09 (0.88; 1.36)	1.27 (0.74; 2.16)	0.93 (0.77; 1.11)
Recent use	0.93 (0.74; 1.16)	1.04 (0.73; 1.47)	1.23 (0.75; 2.00)	0.79 (0.24; 2.56)	0.83 (0.56; 1.22)
New use	1.14 (0.93; 1.40)	0.89 (0.75; 1.06)	1.22 (0.82; 1.81)	1.93 (0.78; 4.77)	1.31 (0.93; 1.84)
Long-term use	0.91 (0.81; 1.02)	0.83 (0.57; 1.20)	1.06 (0.83; 1.35)	1.05 (0.56; 1.99)	0.84 (0.68; 1.03)
Atrial fibrillation or flutter					
Current use	0.97 (0.83; 1.14)	0.96 (0.76; 1.23)	0.86 (0.60; 1.23)	1.12 (0.41; 3.04)	0.95 (0.72; 1.26)
Recent use	0.96 (0.69; 1.34)	1.19 (0.72; 1.96)	1.18 (0.63; 2.21)	1.34 (0.15;11.91)	0.59 (0.30; 1.15)
New use	0.89 (0.64; 1.25)	0.77 (0.46; 1.30)	0.53 (0.23; 1.21)	2.71 (0.64;11.55)	1.05 (0.57; 1.94)

Long-term use	0.99 (0.83; 1.18)	1.02 (0.78; 1.32)	0.97 (0.66; 1.44)	0.57 (0.13; 2.56)	0.92 (0.68; 1.25)
No atrial fibrillation or flutter					
Current use	0.97 (0.88; 1.07)	0.81 (0.67; 0.98)	1.10 (0.93; 1.31)	1.20 (0.84; 1.72)	0.94 (0.79; 1.12)
Recent use	1.01 (0.82; 1.24)	1.08 (0.75; 1.54)	0.95 (0.61; 1.49)	1.03 (0.45; 2.35)	1.01 (0.73; 1.41)
New use	1.12 (0.93; 1.35)	0.79 (0.53; 1.18)	1.22 (0.88; 1.70)	1.32 (0.65; 2.67)	1.29 (0.95; 1.74)
Long-term use	0.92 (0.82; 1.03)	0.81 (0.66; 1.00)	1.07 (0.88; 1.31)	1.15 (0.77; 1.73)	0.84 (0.69; 1.02)
Recent osteoporotic fracture^e					
Current use	1.07 (0.80; 1.42)	0.75 (0.44; 1.29)	1.84 (0.87; 3.86)	-	1.10 (0.68; 1.77)
Recent use	0.40 (0.16; 0.97)	0.18 (0.03; 1.34)	1.28 (0.28; 5.85)	-	0.16 (0.02; 1.20)
New use	1.12 (0.69; 1.81)	0.89 (0.38; 2.05)	1.93 (0.73; 5.10)	-	0.81 (0.28; 2.32)
Long-term use	1.04 (0.74; 1.46)	0.75 (0.39; 1.45)	1.24 (0.43; 3.57)	-	1.16 (0.69; 1.93)
No recent osteoporotic fracture					
Current use	1.00 (0.92; 1.09)	0.91 (0.78; 1.05)	1.07 (0.91; 1.25)	1.09 (0.79; 1.51)	0.98 (0.85; 1.14)
Recent use	1.11 (0.93; 1.32)	1.27 (0.95; 1.71)	1.09 (0.75; 1.57)	0.87 (0.39; 1.95)	1.06 (0.79; 1.43)
New use	1.11 (0.93; 1.32)	0.81 (0.57; 1.14)	1.06 (0.76; 1.47)	1.42 (0.77; 2.61)	1.37 (1.04; 1.81)
Long-term use	0.98 (0.89; 1.07)	0.93 (0.79; 1.10)	1.07 (0.90; 1.27)	1.00 (0.69; 1.45)	0.89 (0.75; 1.06)
Non-recent osteoporotic fracture^f					
Current use	0.97 (0.86; 1.10)	0.90 (0.72; 1.12)	1.01 (0.80; 1.28)	1.41 (0.76; 2.63)	0.93 (0.75; 1.16)
Recent use	1.09 (0.85; 1.41)	1.27 (0.84; 1.92)	0.98 (0.58; 1.67)	0.88 (0.19; 4.01)	0.97 (0.63; 1.50)
New use	1.15 (0.89; 1.48)	0.77 (0.45; 1.32)	1.44 (0.92; 2.26)	1.87 (0.49; 7.09)	1.26 (0.82; 1.94)
Long-term use	0.94 (0.82; 1.08)	0.93 (0.74; 1.18)	0.93 (0.72; 1.21)	1.29 (0.64; 2.59)	0.87 (0.68; 1.11)
No non-recent osteoporotic fracture					
Current use	1.00 (0.90; 1.11)	0.87 (0.72; 1.06)	1.07 (0.87; 1.30)	1.24 (0.85; 1.82)	1.02 (0.84; 1.23)
Recent use	0.96 (0.76; 1.22)	1.03 (0.68; 1.55)	1.10 (0.67; 1.80)	1.21 (0.50; 2.95)	0.94 (0.63; 1.40)
New use	1.06 (0.86; 1.31)	0.87 (0.59; 1.28)	0.88 (0.58; 1.34)	1.61 (0.80; 3.26)	1.02 (0.84; 1.23)
Long-term use	0.97 (0.86; 1.10)	0.87 (0.70; 1.08)	1.13 (0.90; 1.41)	1.13 (0.73; 1.77)	1.30 (0.92; 1.83)
Simple osteoporosis^g					
Current use	0.87 (0.68; 1.10)	0.92 (0.60; 1.42)	1.06 (0.66; 1.70)	0.66 (0.18; 2.37)	0.65 (0.41; 1.03)
Recent use	1.30 (0.88; 1.92)	1.73 (0.86; 3.49)	2.18 (0.77; 6.15)	-	1.14 (0.60; 2.17)
New use	0.67 (0.41; 1.11)	0.71 (0.29; 1.73)	0.79 (0.24; 2.57)	-	0.47 (0.17; 1.33)
Long-term use	0.92 (0.71; 1.19)	0.97 (0.61; 1.55)	1.14 (0.67; 1.91)	0.55 (0.14; 2.09)	0.68 (0.42; 1.12)
No simple osteoporosis					
Current use	1.06 (0.97; 1.15)	0.94 (0.81; 1.10)	1.14 (0.97; 1.34)	1.16 (0.82; 1.64)	1.06 (0.91; 1.23)
Recent use	1.01 (0.83; 1.23)	1.14 (0.82; 1.58)	1.02 (0.69; 1.52)	0.88 (0.36; 2.13)	0.92 (0.66; 1.29)
New use	1.25 (1.05; 1.48)	0.95 (0.68; 1.34)	1.17 (0.85; 1.61)	1.41 (0.74; 2.67)	1.46 (1.10; 1.92)
Long-term use	1.01 (0.91; 1.11)	0.94 (0.79; 1.12)	1.13 (0.94; 1.36)	1.08 (0.72; 1.62)	0.96 (0.81; 1.14)

^aPrescription redemption within 90 days before admission date.

^bPrescription redemption within 90-180 days before admission date.

^cPrescription redemption within 90 days before admission day and no additional prescriptions.

^dPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions prior to this period.

^eFracture \leq 6 months prior to the stroke diagnosis.

^fFracture $>$ 6 months prior to the stroke diagnosis.

^gHospital-diagnosed osteoporosis without fracture.

Abbreviations: AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI, confidence interval.

Table S8. Preadmission use of oral bisphosphonate and 30-day mortality risk and mortality rate ratio; excluding atrial fibrillation and vitamin K antagonist from the multivariate analysis

	Mortality risk % (95% CI)	MRRs (95% CI) Unadjusted	MRRs (95% CI) Adjusted^a
Stroke overall			
No use ^b	13.9 (13.7;14.2)	1 (reference)	1 (reference)
Current use ^c	19.2 (17.9;20.5)	1.42 (1.31; 1.53)	0.97 (0.89; 1.05)
Recent use ^d	20.2 (17.3;23.5)	1.49 (1.26; 1.77)	1.01 (0.85; 1.20)
New use ^e	20.8 (18.0;23.9)	1.55 (1.32; 1.83)	1.07 (0.91; 1.26)
Long-term use ^f	18.7 (17.3;20.3)	1.38 (1.26; 1.51)	0.94 (0.85; 1.03)
AIS			
No use	8.5 (8.2; 8.7)	1 (reference)	1 (reference)
Current use	11.9 (10.4; 13.5)	1.43 (1.24; 1.64)	0.86 (0.74; 1.00)
Recent use	14.7 (11.2; 19.0)	1.80 (1.35; 2.40)	1.11 (0.83; 1.49)
New use	11.5 (8.6; 15.4)	1.39 (1.02; 1.89)	0.80 (0.58; 1.10)
Long-term use	12.0 (10.4; 13.8)	1.44 (1.23; 1.68)	0.87 (0.74; 1.02)
ICH			
No use	34.5 (33.7;35.4)	1 (reference)	1 (reference)
Current use	43.2 (38.8;48.0)	1.37 (1.19; 1.58)	1.06 (0.91; 1.24)
Recent use	43.4 (32.8;55.6)	1.37 (0.96; 1.95)	1.02 (0.71; 1.46)
New use	44.3 (35.1;54.8)	1.42 (1.05; 1.92)	1.12 (0.82; 1.51)
Long-term use	42.9 (37.9;48.3)	1.36 (1.15; 1.60)	1.05 (0.88; 1.25)
SAH			
No use	23.2 (22.0;24.5)	1 (reference)	1 (reference)
Current use	40.3 (31.9;50.0)	1.82 (1.35; 2.45)	1.16 (0.83; 1.62)
Recent use	31.8 (16.6;55.4)	1.51 (0.72; 3.17)	0.96 (0.45; 2.05)
New use	50.0 (32.2;70.9)	2.38 (1.35; 4.20)	1.47 (0.81; 2.65)
Long-term use	37.6 (28.4;48.7)	1.67 (1.18; 2.37)	1.07 (0.73; 1.56)
Unspecified stroke			
No use	14.0 (13.6;14.4)	1 (reference)	1 (reference)
Current use	18.8 (16.6; 21.2)	1.39 (1.21; 1.59)	0.94 (0.82; 1.09)
Recent use	19.5 (15.0; 25.2)	1.42 (1.06; 1.90)	0.92 (0.68; 1.23)
New use	21.7 (17.1; 27.4)	1.63 (1.25; 2.13)	1.21 (0.92; 1.59)
Long-term use	17.9 (15.6; 20.6)	1.32 (1.12; 1.54)	0.87 (0.74; 1.02)

Notes: ^aAdjusted for sex, age groups, recent osteoporotic fracture (≤ 6 months), non-recent osteoporotic fracture (> 6 months), simple osteoporosis (no fracture), myocardial infarction, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, obesity, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease (includes inhalation medications for chronic pulmonary obstructive disease), alcoholism-related diseases, dementia, cancer, and use of cardiovascular drugs (angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor blockers, beta-blockers, calcium channel blockers, diuretics, nitrates, statins, acetylsalicylic acid, clopidogrel, and

vitamin K antagonists), hormone replacement therapy, systemic glucocorticoids, non-steroidal-anti-inflammatory drugs, and selective-serotonin-receptor inhibitors.

^bNo prescription redemption 0-180 days before admission date.

^cPrescription redemption within 90 days before admission date.

^dPrescription redemption within 90-180 days before admission date.

^ePrescription redemption within 90 days before admission day and no additional prescriptions.

^fPrescription redemption within 90 days before admission date and at least 1 additional prescription 90-180 days prior to admission and eventually additional prescriptions before this period.

Abbreviations: MRRs, mortality rate ratios; PS-matched, propensity-score-matched; AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI, confidence interval.