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ORIGINAL ARTICLE

The effectiveness of bisphosphonates vs denosumab in people with dementia or frailty post hip fracture: a multi-database cohort study

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Abstract

Summary *Brief rationale:* The effectiveness of bisphosphonates versus denosumab after hip fracture, especially in people with dementia or frailty, remains unclear. *Main result:* Bisphosphonates were associated with a higher rate of subsequent fracture and a lower mortality rate in men. There are no differences by dementia or frailty status. *Significance of the paper:* Sex may influence antiresorptive treatment choice.

Purpose The relative effectiveness of first-line antiresorptive medications post-hip fracture in people with dementia or frailty is not understood. We investigated the risk of a subsequent fracture and death in people prescribed bisphosphonates or denosumab following hip fracture, including in people with dementia and frailty.

Methods Parallel population-based cohort studies were conducted in Australia, Hong Kong, Taiwan, and the United Kingdom. People aged ≥ 50 prescribed or dispensed a bisphosphonate or denosumab within 60 days of discharge following their first hip fracture were included. Subgroup analyses were conducted for people with dementia, frailty, women, and men. Outcomes were second hip fracture, any subsequent fracture, and death. Inverse probability of treatment weighted Cox and competing risk models were used to estimate hazard ratios (HR) and subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs) for outcomes. Results across jurisdictions were combined using meta-analyses.

Results There were 18,292 bisphosphonate users and 8560 denosumab users. Bisphosphonates versus denosumab were associated with similar rates of second hip fracture (sHR 1.13; 95% CI 0.76–1.69) and mortality (HR 0.99; 95% CI 0.94–1.04), but higher rates of any subsequent fracture (sHR 1.16; 95% CI 1.11–1.21), including in men (sHR1.27; 95% CI 1.15–1.42) but not in women (sHR 1.23; 95% CI 1.00–1.52), or in people with dementia or frailty. Men who used bisphosphonates had lower rates of mortality (HR 0.90; 95% CI 0.81–0.99) than men who used denosumab.

Conclusion Bisphosphonate users had higher rates of subsequent fracture than denosumab users. Mortality rates in men were lower with bisphosphonates than denosumab. There were no significant differences by dementia and frailty status.

Keywords Bisphosphonates · Dementia · Denosumab · Frailty · Hip fractures

Introduction

Successful management of hip fracture involves reducing the risk of second fracture. Minimal trauma osteoporotic fracture predisposes an individual to at least a two-fold risk of second fractures [1]. Bisphosphonates and denosumab are first-line therapy following hip fracture [2, 3]. People adherent to bisphosphonates are less likely to experience a second hip fracture when compared to those who were less adherent and non-users [4]. A recent systematic review reported that bisphosphonates were as effective for older as for younger people [2]. Randomized controlled trials (RCTs) demonstrated denosumab was superior to bisphosphonates in improving bone mineral density in general populations [5]. However, a Danish cohort study reported that denosumab and alendronate, one of the commonly used

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bisphosphonates, were associated with a similar risk of hip or any fracture over three years, regardless of fracture history [6].

One in five people who experience a hip fracture has dementia, and 42% have cognitive impairment [7]. Major fall-related injuries are more common in people with dementia [8]. Second hip fracture is two-fold higher in people with dementia than without dementia [9]. People with dementia are at a 2.5 to threefold increased risk of hip fracture and 50% increased risk of death after hip fracture than people without dementia [10, 11]. A recent single-center study in Australia reported that people with dementia had a higher rate of osteoporosis, were less likely to receive antiresorptive treatment, and had a higher incidence of second fractures and mortality [12].

Current osteoporosis guidelines do not make specific treatment recommendations for people with dementia or those who are frail [1, 13–15]. Frailty relates to the reduced ability of the body to adapt to physiological stressors and is associated with decline across multiple organ systems [16]. When reduced muscle mass and strength (sarcopenia) co-occur with osteoporosis, the risk of hospitalization and death increases [17]. A five-year study of 2005 nursing home residents found that oral bisphosphonates were associated with 27% reduced mortality and a 27% reduced incidence of hip fracture compared to non-use [18]. Nevertheless, no study has directly compared bisphosphonates to denosumab in frail older people. Oral bisphosphonate discontinuation after two years is up to twice as high as denosumab discontinuation in post-menopausal women [19]. Sex May also be an effect-modifier on fracture risk and survival among people with hip fractures. Femoral neck and trochanteric fractures are 77% and 33% more likely in women than men, and the mortality rate is 2.2 times higher in men than women [20].

The objective of this multi-database study was to investigate the risk of a second hip fracture, any subsequent fracture, and death in people prescribed bisphosphonates or denosumab following hip fracture, including in people with dementia and frailty. The study was part of the Four Continents for Dementia (4C4D) study to address evidence gaps arising from the underrepresentation of people with dementia and frailty in RCTs.

Methods

Study design

We conducted parallel population-based cohort studies across four jurisdictions—Australia, Taiwan, Hong Kong, and the United Kingdom (UK). The study was conducted using a distributed network approach with a common study protocol [21]. This means that each jurisdiction analyzed its data using a common study protocol, and only final results were shared with the primary investigator.

Data sources

In Australia, we analyzed the Victorian Admitted Episodes Dataset (VAED). Victoria has a population of 6.7 million people and is Australia's second most populous state. The VAED includes demographic, administrative, and diagnostic information on episodes of care in Victorian public and private hospitals, rehabilitation centers, extended care facilities, and day procedure centers [22]. The VAED was linked to medication dispensing data through Australia's Pharmaceutical Benefits Scheme (PBS). The PBS subsidizes medications dispensed in community pharmacies, in private hospitals, and for inpatients at discharge and outpatients in public hospitals for all Australian citizens, permanent residents, and visitors from countries with reciprocal healthcare agreements. Data were also linked to the National Death Index. Data linkage was performed by the Australian Institute of Health and Welfare (AIHW). Ethics approval was obtained from the AIHW Ethics Committee (EO2018-4–468) and Monash University Human Research Ethics Committee (14339).

In Taiwan, we analyzed the National Health Insurance Research Database (NHIRD) [23]. NHIRD contains medical health records for more than 99% of the 23 million Taiwanese citizens, including recorded diagnoses and prescription claims from outpatient, emergency room, and inpatient settings. The study was approved by the National Cheng Kung University Hospital Institutional Review Board (B-ER-107–378).

In Hong Kong, we analyzed data from the Clinical Data Analysis and Reporting System. This territory-wide database is maintained by the Hong Kong Hospital Authority, the statutory body that manages all public hospitals, their associated ambulatory clinics, primary care clinics, and emergency departments for all seven million residents [24]. Diagnostic and medication dispensing data were available for all public hospitals and their associated facilities. The study was approved by institutional review boards of the University of Hong Kong and Hong Kong Hospital Authority (UW19-154 and UW 22–076).

In the UK, we analyzed data from the UK IQVIA Medical Research Data (IMRD, formerly known as The Health Improvement Network [THIN]) [25]. IMRD includes > 18 million anonymized people visiting across > 800 general practices. Data included demographics, diagnoses, prescribing records, referrals, laboratory tests, immunizations, and Townsend (deprivation) scores. Ethical approval was granted by THIN Scientific Review Committee (22SRC007).

Inclusion and exclusion criteria

We included people aged ≥ 50 with a first recorded diagnosis of hip fracture (*index hip fracture*; diagnosis codes in Appendix Table 1) treated as a primary diagnosis in hospital between 1 July 2013 and 30 March 2018 in Australia, 1 January 2013 to 31 December 2018 in Taiwan, 1 January 2013 to 31 December 2017 in Hong Kong, and 1 January 2011 to 31 December 2020 in the UK. We used a 5-year washout period to define incident hip fracture. Individuals were included if they were prescribed or dispensed a bisphosphonate or denosumab within 60 days following the discharge date of index hip fracture hospitalization (Fig. 1). People who died within 60 days of the discharge date of index hip fracture hospitalization or who had a recorded cancer diagnosis in the one-year prior to index hip fracture were excluded.

Definition of dementia and frailty

We included people with all types of dementia, including Alzheimer's disease, vascular dementia, mixed dementias, and Lewy Body dementia. Dementia was defined using at least one recorded diagnosis of dementia or dispensing or prescribing record of any dementia medication (cholinesterase inhibitor, memantine, and antipsychotic reimbursed for behavioral symptoms of dementia in Australia) prior to or at index hip fracture (Appendix Table 1). Frailty was identified using the validated Hospital Frailty Risk Score (HFRS) where frail individuals were defined as those with a HFRS > 15 [26]. HFRS is specifically developed for administrative data using International Classification of Diseases 10th edition (ICD-10) codes. HFRS were calculated using recorded diagnoses within two years prior to or at index hip fracture.

Exposure and comparator

The exposure variable was the prescribing or dispensing of a bisphosphonate. The active comparison group was people prescribed or dispensed denosumab. We used a landmark period of 60 days starting from the index hip fracture to define medication exposure (Fig. 1). The exposure was defined using jurisdiction-specific medication codes [Anatomical Therapeutic Chemical (ATC) or British National Formulary (BNF) codes] from dispensing records or prescribing data (Appendix Table 2). People prescribed or dispensed both bisphosphonate and denosumab within the landmark period were excluded.

Potential confounders

Potential confounders included basic demographic (e.g., age and sex), calendar year of index hip fracture, recent fall (defined as a fall-related emergency department visit in the past year), and other recorded comorbidities prior to and on the date of index hip fracture (Appendix Tables 3 and 4). Comorbidities were identified in the fixed and equal 7-year period prior to and on the index hip fracture. Potential medication confounders prescribed or dispensed one year prior to or on the date of index hip fracture were identified (Appendix Table 2). These medications include other anti-fracture medications and medications that may potentially affect fracture risk or bone mineral density.

Outcomes

The outcome variables were a second hip fracture (as a primary diagnosis), any subsequent fracture (as a primary diagnosis), and all-cause death during follow-up. The diagnosis codes used to define the outcomes are provided in Appendix Tables 4 and 5. Patients were followed from the end of the landmark period (60 days after the discharge from index hip fracture) until the earliest recording of a second hip fracture, death, date of transfer out of practice (for UK), date of last data collection from the practice (for UK), or end of data period, whichever came first.

Statistical analyses

Baseline characteristics of patients prescribed or dispensed a bisphosphonate or denosumab on or within 60 days after the index hip fracture were compared using standardized mean differences (SMD). Number of events and median time to event for those in the exposure and comparator groups were recorded for each jurisdiction. We conducted a propensity score (PS) analysis using the inverse probability treatment weighting (IPTW) to adjust for potential bias arising from treatment allocation [27]. The PS was estimated using a logistic regression model which includes all potential confounders as predictors for the treatment group. The stabilized weight was then calculated for each person as 1/PS for those in the treated group and 1/1-PS for those in the comparison group, multiplied by the Marginal probability of receiving the respective treatment. Extreme weight values were truncated at the 5th and 95th percentiles of the distribution. Finally, we used Cox Proportional Hazards regression models weighted by IPTW to examine associations between osteoporosis medication use and the risk of death. Weighted Fine and Gray competing risk models were used to estimate the risk of second hip fracture and any subsequent fracture, with death as a competing event. Hazard ratios (HR), and sub-distribution

Table 1 Baseline characteristics of cohorts

	Australia (*N* = 3936)				Hong Kong (*N* = 1946)				Taiwan (*N* = 14,486)				UK (*N* = 6484)		
	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab	
	N = 2155	*N* = 1781	SMD, %	SMD, %	*N* = 1822	*N* = 124	SMD, %	SMD, %	*N* = 7876	*N* = 6610	SMD, %	SMD, %	*N* = 6439	N = 45N = 45	SMD, %
Socio-demographic variables, n (%)															
Sex, female	1724 (80.0)	1437 (80.7)	− 1.72	4.10	1418 (77.8)	107 (86.3)	− 22.19	0.87	6043 (76.7)	5171 (78.2)	− 3.60	− 0.19	5214 (81.0)	42 (93.3)	− 37.58
Age, years mean (SD)	NA	NA	NA	NA	80.56 (8.24)	82.19 (7.50)	20.79	− 0.89	NA	NA	NA	NA	81.5 (8.8)	81.3 (7.8)	2.63
50–59	131 (6.1)	102 (5.7)	1.49	− 0.82	30 (1.6)	3 (2.4)	NA	NA	178 (2.3)	134 (2.0)	1.61	1.24	140 (2.2)	0	21.08
60–69	354 (16.4)	284 (16.0)	1.31	2.69	174 (9.5)	4 (3.2)	NA	NA	893 (11.3)	703 (10.6)	2.25	0.82	436 (6.8)	3 (6.7)	0.42
70–79	905 (42.0)	742 (41.7)	0.68	− 0.75	498 (27.3)	25 (20.2)	NA	NA	2361 (30.0)	1982 (30.0)	− 0.02	− 1.10	1570 (24.4)	14 (31.1)	− 15.07
80+	765 (35.5)	653 (36.7)	− 2.43	− 0.88	1120 (61.5)	92 (74.2)	NA	NA	4444 (56.4)	3791 (57.4)	− 1.87	0.13	4267 (66.3)	28 (62.2)	8.48
Year of index date, n (%)															
2011	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	511 (7.9)	1 (2.2)	26.95
2012	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1105 (17.2)	3 (6.7)	33.81
2013*	361 (16.8)	62 (3.5)	45.11	− 1.22	328 (18.0)	15 (12.1)	16.57	− 4.12	1468 (18.6)	442 (6.7)	36.53	20.70	1049 (16.3)	9 (20.0)	− 7.74
2014	617 (28.6)	233 (13.1)	38.99	0.90	426 (23.4)	23 (18.5)	11.89	1.99	1413 (17.9)	667 (10.1)	22.76	9.63	963 (15.0)	8 (17.8)	− 11.55
2015	506 (23.5)	338 (19.0)	11.03	0.33	362 (19.9)	22 (17.7)	5.44	4.7	1350 (17.1)	1029 (15.6)	4.25	− 0.64	709 (11.0)	11 (24.4)	− 33.34
2016	363 (16.8)	432 (24.3)	− 18.42	− 0.49	376 (20.6)	23 (18.5)	5.26	− 3.53	1367 (17.4)	1180 (17.9)	− 1.30	− 2.19	540 (8.4)	4 (8.9)	− 0.27
2017	274 (12.7)	540 (30.3)	− 43.86	0.44	328 (18.0)	15 (12.1)	34.78	0.95	1246 (15.8)	1707 (25.8)	− 24.83	− 9.23	541 (8.4)	0 (0.0)	42.65
2018*	34 (1.6)	176 (9.9)	− 36.32	− 0.47	NA	NA	NA	NA	1032 (13.1)	1585 (24.0)	− 28.26	− 11.45	423 (6.6)	2 (4.4)	10.52
2019	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	333 (5.2)	4 (8.9)	− 19.86
2020	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	265 (4.1)	3 (6.7)	− 9.78
History of falls	2019 (93.7)	1675 (94.1)	− 1.50	− 0.12	431 (23.7)	27 (21.8)	4.49	4.23	75 (1.0)	102 (1.5)	− 5.32	− 3.57	1196 (18.6)	12 (26.7)	− 19.43
Previous vertebral fracture**	134 (6.2)	91 (5.1)	4.80	− 0.30	110 (6.0)	16 (12.9)	− 23.61	− 2.85	2339 (29.7)	1623 (24.6)	11.59	4.56	202 (3.1)	4 (8.9)	− 24.37

Table 1 (continued)

	Australia (*N* = 3936)				Hong Kong (*N* = 1946)				Taiwan (*N* = 14,486)				UK (*N* = 6484)		
	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab	
	N = 2155	*N* = 1781	SMD, %	SMD, %	*N* = 1822	*N* = 124	SMD, %	SMD, %	*N* = 7876	*N* = 6610	SMD, %	SMD, %	*N* = 6439	N = 45N = 45	SMD, %
Previous other fracture	563 (26.1)	440 (24.7)	3.26	−1.55	389 (21.4)	33 (26.6)	−12.35	−3.18	3058 (38.8)	2465 (37.3)	3.16	−0.08	3298 (51.2)	28 (62.2)	−22.35
Comorbidities, *n* (%)															
Cardiovascular disease***	1049 (48.7)	862 (48.4)	0.56	0.98	858 (47.1)	71 (57.3)	−20.46	−3.83	6865	5786	−1.11	0.35	4090 (63.5)	26 (57.8)	11.77
Major bleeding	570 (26.5)	460 (25.8)	1.42	1.73	195 (10.7)	17 (13.7)	−9.2	10.05	3545	3278	−9.19	−3.82	705 (10.9)	8 (17.8)	−19.56
Obesity	19 (0.9)	17 (1.0)	−0.76	−0.45	5 (0.3)	3 (2.4)	−18.69	1.03	45 (0.6)	29 (0.4)	1.87	0.64	13 (0.2)	0 (0)	6.12
CKD	475 (22.0)	470 (26.4)	−10.16	1.00	57 (3.1)	6 (4.8)	−8.75	−7.57	1250 (15.9)	1798 (27.2)	−27.83	−12.21	1711 (26.6)	17 (37.8)	−24.16
Diabetes	478 (22.2)	446 (25.0)	−6.74	−0.48	356 (19.5)	32 (25.8)	−15.01	−0.46	4039 (51.3)	3487 (52.8)	−2.94	−0.82	1164 (18.1)	4 (8.9)	27.15
COPD/asthma	232 (10.8)	189 (10.6)	0.50	0.28	72 (4.0)	7 (5.6)	−7.93	−9.04	2976 (37.8)	2438 (36.9)	1.87	0.78	1261 (19.6)	7 (15.6)	10.60
Epilepsy	57 (2.7)	27 (1.5)	7.92	1.76	22 (1.2)	5 (4.0)	−17.75	7.14	277 (3.5)	196 (3.0)	3.12	0.50	70 (1.1)	0 (0)	14.83
Arthritis	318 (14.8)	231 (13.0)	5.17	−1.86	181 (9.9)	18 (14.5)	−14.02	−7.24	5714 (72.5)	4692 (71.0)	3.48	1.28	143 (2.2)	3 (6.7)	−21.70
Hyperthyroidism	47 (2.2)	25 (1.4)	5.86	0.38	20 (1.1)	1 (0.8)	3	−5.02	235 (3.0)	230 (3.5)	−2.80	−1.30	NA	NA	NA
Hyperparathyroidism	7 (0.3)	20 (1.1)	−9.43	−3.97	5 (0.3)	0 (0.0)	−7.26	−14.47	11 (0.1)	40 (0.6)	−7.65	−0.01	NA	NA	NA
Alcohol misuse	71 (3.3)	64 (3.6)	−1.64	0.08	7 (0.4)	0 (0.0)	−5.49	−13.07	67 (0.9)	45 (0.7)	1.95	0.03	NA	NA	NA
Osteoporosis	553 (25.7)	478 (26.8)	−2.68	1.61	250 (13.7)	25 (20.2)	−17.23	6.45	3601 (45.7)	2635 (39.9)	11.86	5.53	NA	NA	NA
Blindness/visual impairment	53 (2.5)	32 (1.8)	4.59	2.05	13 (0.7)	2 (1.6)	−8.4	3.26	1610 (20.4)	1421 (21.5)	−2.59	−0.39	NA	NA	NA
Prior medications, n (%)															
Prior use of anti-fracture medications****	1698 (78.8)	1024 (57.5)	46.95	−1.00	323 (17.7)	42 (33.9)	−13.12	2.83	NA	NA	NA	NA	1892 (29.4)	15 (33.3)	−8.52
Antipsychotics	186 (8.6)	151 (8.5)	0.55	−0.09	85 (4.7)	6 (4.8)	−0.82	12.09	1094 (13.9)	911 (13.8)	0.31	1.13	304 (4.7)	4 (8.9)	−16.61

Table 1 (continued)

	Australia ($N=3936$)				Hong Kong ($N=1946$)				Taiwan ($N=14,486$)				UK ($N=6484$)		
	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab	
	$N=2155$	$N=1781$	SMD, %	SMD, %	$N=1822$	$N=124$	SMD, %	SMD, %	$N=7876$	$N=6610$	SMD, %	SMD, %	$N=6439$	N = 45N = 45	SMD, %
Antidepressants	774 (35.9)	643 (36.1)	−0.39	−0.90	134 (7.4)	17 (13.7)	−20.81	4.75	1417 (18.0)	1117 (16.7)	2.88	2.66	2095 (32.5)	21 (46.7)	−29.20
Benzodiazepines	625 (29.0)	452 (25.4)	8.15	0.01	NA	NA	NA	NA	3642 (42.6)	3016 (45.6)	1.23	0.14	6 (0.1)	0 (0)	4.32
Antiepileptics	148 (6.9)	101 (5.7)	4.94	−1.01	NA	NA	NA	NA	923 (11.7)	848 (12.8)	−3.38	−1.71	93 (1.4)	1 (2.2)	−5.80
Cardiac glycosides/ antiarrhythmics, etc	467 (21.7)	354 (19.9)	4.42	0.15	32 (1.8)	6 (4.8)	−17.33	2.33	1161 (14.7)	1131 (17.1)	−6.48	−1.77	268 (4.2)	3 (6.7)	−10.06
Calcium channel blockers	708 (32.9)	612 (34.4)	−3.19	−0.35	948 (52.0)	73 (58.9)	−13.8	5.59	3150 (40.0)	2700 (40.8)	−1.74	0.62	1893 (29.4)	11 (24.4)	11.19
RAAS	1274 (59.1)	1095 (61.5)	−4.83	0.82	536 (29.4)	43 (34.7)	−11.29	−0.82	3229 (41.0)	2917 (44.1)	−6.34	−2.43	2526 (39.2)	15 (33.3)	12.29
Vasodilators	0 (0)	0 (0)	0.00	0.00	11 (0.6)	2 (1.6)	−9.65	4.57	1309 (16.6)	1159 (17.5)	−2.43	−1.00	10 (0.2)	0 (0)	5.58
Beta-blocking agents	648 (30.1)	527 (29.6)	1.05	1.50	392 (21.5)	36 (29.0)	−17.36	8.85	2069 (26.3)	1798 (27.2)	−2.10	0.44	1631 (25.3)	11 (24.4)	2.05
Diuretics	868 (40.3)	721 (40.5)	−0.42	1.63	211 (11.6)	20 (16.1)	−13.19	6.95	1581 (20.1)	1470 (22.2)	−5.30	−1.56	2094 (32.5)	15 (33.3)	−1.73
Insulin or sulfonylureas	256 (11.9)	230 (12.9)	−3.14	1.47	287 (15.8)	23 (18.5)	−7.42	0.67	NA	NA	NA	NA	387 (6.0)	0 (0)	35.76
Other GLDs	315 (14.6)	282 (15.8)	−3.39	−0.11	369 (20.3)	23 (18.5)	4.31	4.6	NA	NA	NA	NA	710 (11.0)	2 (4.4)	24.83
Antihypertensives	134 (6.2)	111 (6.2)	−0.06	0.76	NA	NA	NA	NA	349 (4.4)	401 (6.1)	−7.34	−3.17	323 (5.0)	2 (4.4)	2.69
Paracetamol	1372 (63.7)	912 (51.2)	25.40	−1.08	NA	NA	NA	NA	4840 (61.5)	4014 (60.7)	1.49	0.23	2461 (38.2)	19 (42.2)	−8.17
Opioids	1506 (69.9)	1245 (69.9)	−0.04	−1.77	NA	NA	NA	NA	1597 (20.3)	1439 (21.8)	−3.67	−0.86	2430 (37.7)	24 (53.3)	−31.71
Other analgesics	1446 (67.1)	1005 (56.4)	22.09	−0.71	NA	NA	NA	NA	5082 (64.5)	4192 (63.4)	2.30	0.30	2485 (38.6)	19 (42.2)	−7.40
NSAIDs	399 (18.5)	332 (18.6)	−0.32	−1.97	89 (4.9)	3 (2.4)	13.17	7.44	5187 (65.9)	4077 (61.7)	8.70	3.21	711 (11.0)	6 (13.3)	−7.01
TCA	204 (9.5)	147 (8.3)	4.27	−0.76	59 (3.2)	9 (7.3)	−18.1	4.63	389 (4.9)	304 (4.6)	1.60	1.29	713 (11.1)	8 (17.8)	−19.17
Pregabalin	241 (11.2)	222 (12.5)	−3.97	0.90	NA	NA	NA	NA	54 (0.7)	46 (0.7)	−0.12	0.40	157 (2.4)	0 (0)	22.36
Glucocorticoids	401 (18.6)	348 (19.5)	−2.37	0.57	56 (3.1)	5 (4.0)	−5.18	8.96	1551 (19.7)	1274 (19.3)	1.06	0.26	853 (13.2)	6 (13.3)	−0.25

Table 1 (continued)

	Australia (*N* = 3936)				Hong Kong (*N* = 1946)				Taiwan (*N* = 14,486)				UK (*N* = 6484)		
	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab		Weighted	BP	Dmab	
	N = 2155	*N* = 1781	SMD, %	SMD, %	*N* = 1822	*N* = 124	SMD, %	SMD, %	*N* = 7876	*N* = 6610	SMD, %	SMD, %	*N* = 6439	N = 45N = 45	SMD, %
GnRH agonists	21 (1.0)	12 (0.7)	3.33	1.47	NA	NA	NA	NA	0 (0)	0 (0)	0.00	0.00	28 (0.4)	1 (2.2)	−15.66
Aromatase inhibitors	11 (0.5)	18 (1.0)	−5.76	−0.46	NA	NA	NA	NA	0 (0)	0 (0)	0.00	0.00	20 (0.3)	0 (0)	7.89
Methotrexate	66 (3.1)	62 (3.5)	−2.35	−0.61	NA	NA	NA	NA	0 (0)	0 (0)	0.00	0.00	0 (0)	0 (0)	0.00
Cyclosporine	<5*****	<5*****	1.34	0.96	3 (0.2)	1 (0.8)	−9.24	−3.24	5 (0.1)	5 (0.1)	−0.46	−0.02	1 (0.0)	0 (0)	1.76
Tacrolimus	7 (0.3)	<5	3.15	1.11	1822 (100.0)	124 (100.0)	−9.24	−3.24	0 (0)	0 (0)	0.00	0.00	11 (0.2)	0 (0)	−5.85
Proton pump inhibitors	1128 (52.3)	974 (54.7)	−4.70	−0.87	235 (12.9)	30 (24.2)	−29.37	−1.67	650 (8.3)	569 (8.6)	−1.28	−0.16	2678 (41.6)	21 (46.7)	10.24
H_2 antagonists	101 (4.7)	109 (6.1)	−6.34	−0.79	109 (6.0)	4 (3.2)	13.18	0.54	2265 (28.8)	1839 (27.8)	2.08	0.85	307 (4.8)	6 (13.3)	30.19
Antacids	33 (1.5)	14 (0.8)	6.97	−1.25	NA	NA	NA	NA	115 (1.5)	90 (1.4)	0.84	−0.49	0 (0)	0 (0)	0.00

BP bisphosphonates, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *Dmab* denosumab, *GnRH* gonadotropin-releasing hormone, *GLD* glucose-lowering drug, *NA* data not available, *NSAID* non-steroidal anti-inflammatory drugs, *GnRH* gonadotropin-releasing hormone, *RAAS* renin–angiotensin–aldosterone system inhibitors, *SD* standard deviation, *TCA* tricyclic antidepressants

*In Australia, data were only available for the second half of 2013 and the first quarter of 2018

**Previous vertebral fracture includes vertebrae, spine, and neck

***Cardiovascular disease includes myocardial infarction, stroke, hypertension, atrial fibrillation, heart failure

****Includes bisphosphonates, denosumab, teriparatide, strontium ranelate, raloxifene (women only), hormone replacement therapy (estrogen/progestogen; women only), tibolone (women only), hormone replacement therapy (androgens; men only)

*****Numbers less than five were not permitted to be reported from Australian data

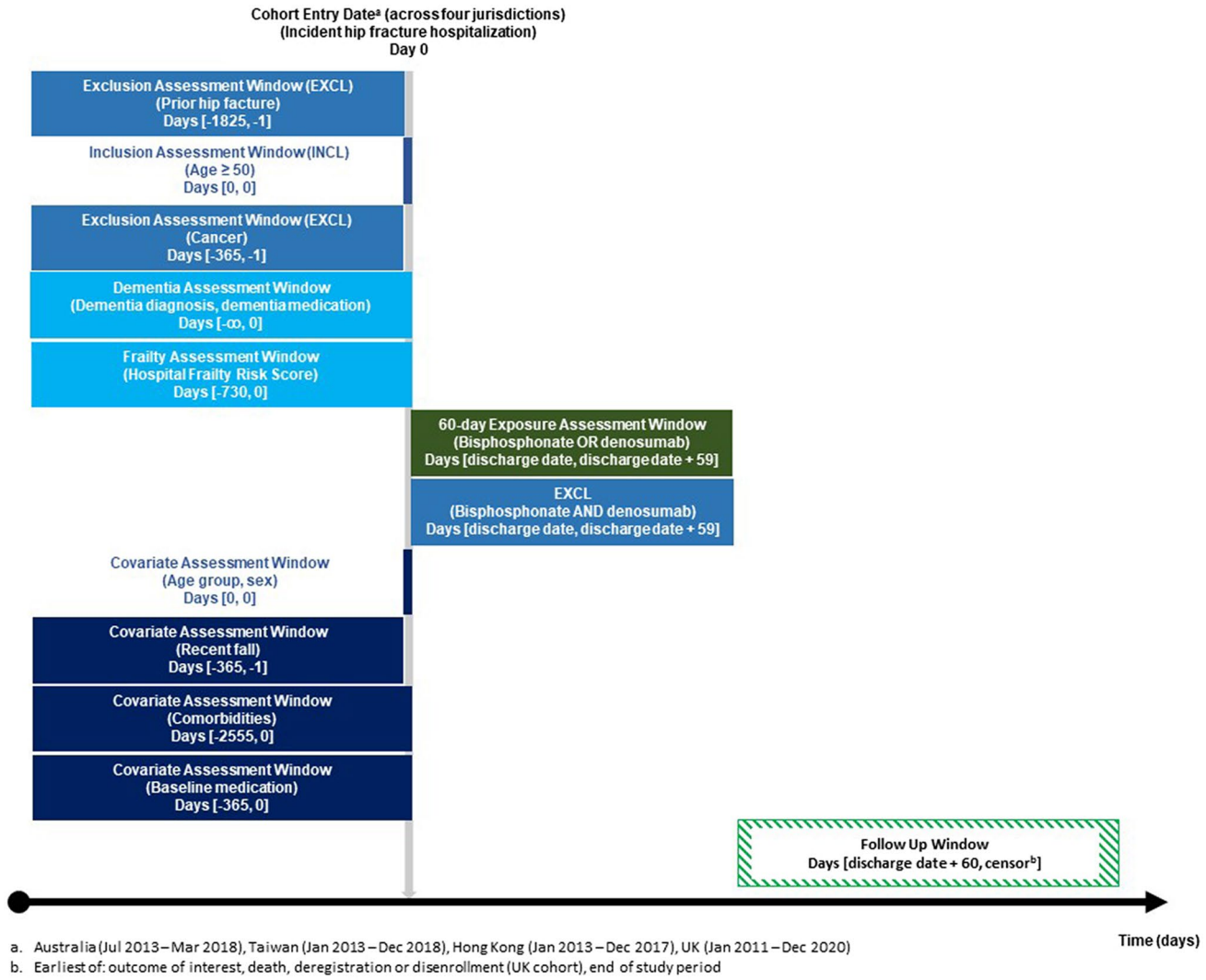

Fig. 1 Illustration of the study design

hazard ratios (sHR) from the competing risk models, with their 95% confidence intervals (95% CIs) from each jurisdiction were pooled to produce an overall estimate of the risks of the three outcomes using random effects model. The models were based on DerSimonian and Laird (DL) method to investigate between-jurisdiction variance. Heterogeneity between countries was assessed using I^2 and prediction intervals. Although it was anticipated that subgroup analyses would be performed for all four sites, due to the low number of denosumab users in the UK ($n = 45$), it was not possible to perform survival analyses in the primary and subgroup analyses. Similarly, subgroup analyses for people with dementia, frailty, and men and women in Hong Kong were not conducted, given the small number of denosumab users ($n = 124$).

Results

Cohort description

Overall, 26,852 people were included in the study (3,936 in Australia, 1,946 in Hong Kong, 14,486 in Taiwan, and 6,484 in the UK) (Fig. 2, Table 1). The proportion of people with dementia ranged from 8.3% in Hong Kong to 17.5% in the UK (Table 2). The proportion of people who were frail ranged from 0.5% in the UK to 17.0% in Taiwan (Table 2). In Australia and Taiwan, 54.8% and 54.4% of people received bisphosphonates, while in Hong Kong and the UK, 93.6% and 99.3% received bisphosphonates. Approximately 80% of each cohort consisted of women.

Table 2 Number of events and median time to event; second hip fracture, second any fracture and all-cause mortality

		Second hip fracture		Any subsequent fracture*		All-cause mortality	
	N (% of region's cohort)	Number of events (%)	Median time to event (days)	Number of events (%)	Median time to event (days)	Number of events (%)	Median time to event (days)
Australia							
Primary cohort	**3936 (100)**						
Bisphosphonate	2155 (54.8)	232 (10.8)	438.5	425 (19.7)	444.0	652 (30.3)	593.0
Denosumab	1781 (45.3)	77 (4.3)	261.0	181 (10.2)	203.5	345 (19.4)	433.0
People with dementia	**576 (14.6)**						
Bisphosphonate	310 (53.8)	28 (9.0)	263.0	51 (16.5)	345.5	156 (50.3)	537.0
Denosumab	266 (46.2)	11 (4.1)	207.0	20 (7.5)	313.0	74 (27.8)	361.5
People with frailty	**426 (10.8)**						
Bisphosphonate	231 (54.2)	24 (10.4)	385.5	43 (18.6)	341.0	111 (48.1)	450.0
Denosumab	195 (45.8)	10 (5.1)	109.5	18 (9.2)	218.5	58 (29.7)	299.5
Women	**3161 (80.3)**						
Bisphosphonate	1724 (54.5)	185 (10.7)	430.0	346 (20.1)	415.0	497 (28.8)	579.0
Denosumab	1437 (45.5)	65 (4.5)	264.0	153 (10.7)	297.0	268 (18.7)	454.0
Men	**775 (19.7)**						
Bisphosphonate	431 (55.6)	47 (10.9)	444.0	431 (55.6)	381.0	155 (36.0)	605.0
Denosumab	344 (44.4)	12 (3.5)	203.5	344 (44.4)	241.5	77 (22.4)	391.0
Hong Kong							
Primary cohort	**1946 (100.0)**						
Bisphosphonate	1822	178 (9.8)	251.0	382 (21.0)	408.0	372 (20.4)	635.5
Denosumab	124	10 (8.1)	270.5	18 (14.5)	273.0	22 (17.7)	495.0
People with dementia	**162 (8.3)**						
Bisphosphonate	145	14 (9.7)	224.0	25 (17.2)	400.0	61 (42.1)	484.0
Denosumab	17	3 (17.6)	232	4 (23.5)	139.0	5 (29.4)	642.0
People with frailty	**59 (3.0)**						
Bisphosphonate	51	4 (7.8)	147.0	8 (15.7)	569.5	27 (52.9)	679.0
Denosumab	8	1 (12.5)	232.0	2 (25.0)	139.0	3 (37.5)	642.0
Women	**1525 (78.4)**						
Bisphosphonate	1418	138 (9.7)	258.5	317 (22.4)	423.0	242 (17.1)	606.5
Denosumab	107	9 (8.4)	309.0	15 (14.0)	352.0	19 (17.8)	636.0
Men	**421 (21.6)**						
Bisphosphonate	404	40 (9.9)	233.0	65 (16.1)	273.0	130 (32.2)	679.0
Denosumab	17	1 (5.9)	232.0	3 (17.6)	144.0	3 (17.6)	354.0
Taiwan							
Primary cohort	**14,486 (100.0)**						
Bisphosphonate	7876	362 (4.6)	163.0	2819 (35.8)	442.5	1808 (23.0)	308.5
Denosumab	6,610	237 (3.6)	135.0	1766 (26.7)	345.0	1214 (18.4)	214.0
People with dementia	**1691 (11.7)**						
Bisphosphonate	919	65 (7.1)	119.0	308 (33.5)	426.0	235 (25.6)	335.0
Denosumab	772	31 (4.0)	104.0	205 (26.6)	324.5	135 (17.5)	212.0
People with frailty	**2462 (17.0)**						
Bisphosphonate	1231	54 (4.4)	126.0	432 (35.1)	352.0	340 (27.6)	237.5
Denosumab	1231	41 (3.3)	45.0	341 (27.7)	274.0	265 (21.5)	164.0

Table 2 (continued)

		Second hip fracture		Any subsequent fracture*		All-cause mortality	
	N (% of region's cohort)	Number of events (%)	Median time to event (days)	Number of events (%)	Median time to event (days)	Number of events (%)	Median time to event (days)
Women	**11,214 (77.4)**						
Bisphosphonate	6043	298 (4.9)	174.0	2289 (37.9)	444.0	1225 (20.3)	347.0
Denosumab	5171	199 (3.8)	148.0	1493 (28.9)	358.0	889 (17.2)	232.0
Men	**3272 (22.6)**						
Bisphosphonate	1833	64 (3.5)	128.0	530 (28.9)	434.0	583 (31.8)	268.0
Denosumab	1439	38 (2.6)	99.0	273 (19.0)	310.0	325 (22.6)	164.0
UK							
Primary cohort	**6484 (100.0)**						
Bisphosphonate	6439	396 (6.2)	376.0	862 (13.4)	517.5	1792 (27.8)	674.5
Denosumab	45	3 (6.7)	72.0	7 (15.6)	1,026.0	10 (22.2)	550.5
People with dementia	**1135 (17.5)**						
Bisphosphonate	1125	69 (6.1)	294.0	119 (10.6)	308.0	465 (41.3)	462.0
Denosumab	10	1 (10.0)	0	1 (10.0)	297	5 (50.0)	292.0
People with frailty	**30 (0.5)**						
Bisphosphonate	30	2 (6.7)	126.5	5 (16.7)	488.0	8 (26.7)	410.5
Denosumab	0	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Women	**5256 (81.1)**						
Bisphosphonate	5214	334 (6.4)	416.0	737 (14.1)	535.0	1380 (26.5)	705.5
Denosumab	42	2 (4.8)	463.5	7 (16.7)	1026.0	9 (21.4)	661.0
Men	**1228 (18.9)**						
Bisphosphonate	1225	62 (5.1)	244.0	125 (10.2)	452.0	412 (33.6)	575.0
Denosumab	3	1 (33.3)	72.0	0 (0.0)	–	1 (33.3)	121.0

*Any other fracture from Taiwan was identified using both inpatient and outpatient records

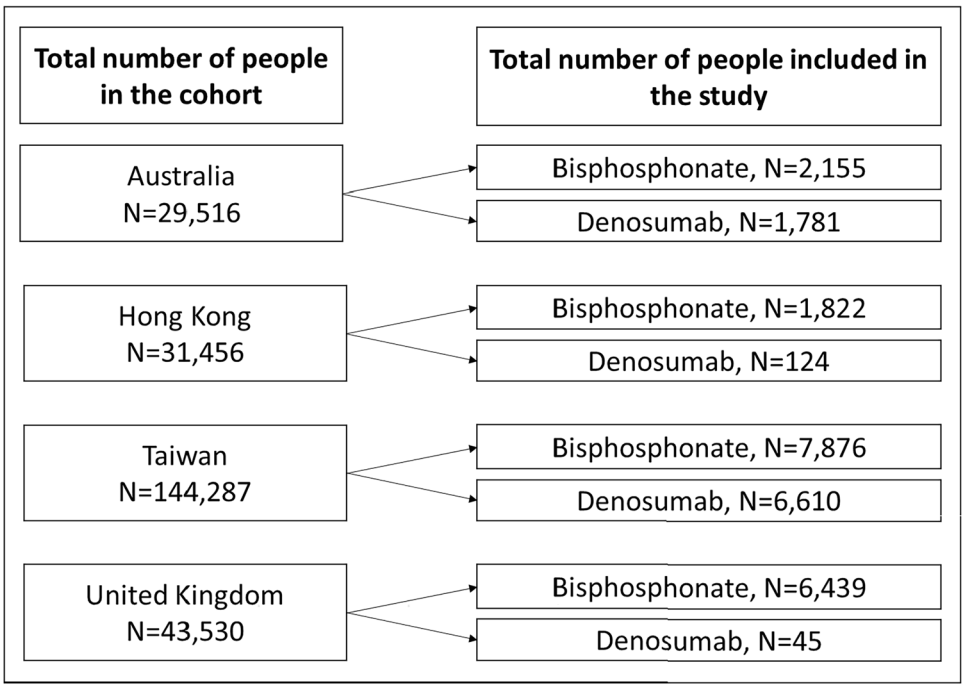

Fig. 2 Flowchart including number of individuals in each cohort before and after application of exclusion criteria

Comorbidities were well balanced between bisphosphonate and denosumab cohorts within each jurisdiction (SMDs < 10%). An exception was chronic kidney disease (CKD) for which the unweighted SMDs in three jurisdictions indicated higher proportions of denosumab users with CKD compared to bisphosphonate users (− 10.16% in Australia, − 27.83% in Taiwan, and − 24.16% in the UK). Heterogeneity existed for recent falls (Taiwan 1.2% vs. Australia 93.9%) and previous vertebral fractures (UK 3.2% vs. Taiwan 27.4%). After IPTW, most baseline covariates were satisfactorily balanced (weighted SMD < 10% difference). In Taiwan, a higher proportion of bisphosphonate users started follow-up in 2013 (weighted SMD, 20.70%), and a lower proportion in 2018 (weighted SMD, − 11.45%), when compared to denosumab users after IPTW.

Proportions of second hip fracture, any subsequent fracture, and death

The proportion of second hip fracture during follow-up was higher among bisphosphonate users (ranging from 4.6% in Taiwan to 10.8% in Australia) than among denosumab users (ranging from 3.6% in Taiwan to 8.1% Hong Kong) (Table 2). Between 13.4% (UK) and 35.8% (Taiwan) of bisphosphonate users experienced any fracture during follow-up, which was higher than for denosumab users (ranging from 10.2% in Australia to 26.7% in Taiwan). Between 20.4% (Hong Kong) and 30.3% (Australia) of bisphosphonate users and between 17.7% (Hong Kong) and 22.2% (UK) of denosumab users died during follow-up.

Rates of second hip fracture, any subsequent fracture, and death

Pooled meta-analysis indicated that bisphosphonate and denosumab users had a similar rate of second hip fracture (sHR 1.13; 95% CI 0.76–1.69) (Fig. 3A). Results were similar across dementia (sHR 1.26; 95% CI 0.94–1.69), frailty (sHR 1.15; 95% CI 0.86–1.52), women (sHR 1.28; 95% CI 0.78–2.09) and men (sHR 1.31; 95% CI 0.84–2.05). The rate of second hip fracture was higher among Australian bisphosphonate versus denosumab users in the primary cohort (sHR 1.65; 95% CI 1.26–2.15). This higher rate of second hip fracture was also evident among women in Australia (sHR 1.67; 95% CI 1.25–2.24).

Bisphosphonate users had a 25% higher rate of any subsequent fracture compared to denosumab users in the primary cohort (sHR 1.25; 95% CI 1.07–1.46) (Fig. 3b). This association was also evident among men (sHR 1.28; 95% CI 1.15–1.42). The association did not exist in people with dementia (sHR 1.30; 95% CI 0.74–2.29), people who were frail (sHR 1.10; 95% CI 0.99–1.22) and in women (sHR 1.23; 95% CI 1.00–1.52). In Australia, people with dementia who used bisphosphonates had a two–fold higher rate of subsequent fracture than people with dementia who used denosumab (sHR 1.90; 95% CI 1.02–3.51).

People who used bisphosphonates and denosumab had a similar rate of all–cause mortality in the primary cohort (HR 0.99; 95% CI 0.94–1.04) (Fig. 3c). This was also true for people with dementia (HR 1.11; 95% CI 0.96–1.28) and people who were frail (HR 0.93; 95% CI 0.83–1.05) and in women (HR 0.96; 95% CI 0.90–1.02). Men who used bisphosphonates had a 10% lower rate of all–cause mortality than men who used denosumab (HR 0.90; 95% CI 0.81–0.99).

Discussion

This international multi-database study conducted across four jurisdictions found no difference in the risk of second hip fracture or death in bisphosphonate and denosumab users. However, bisphosphonate use was associated with a 25% higher rate of subsequent fracture compared with denosumab use. There was a non-significant trend toward a higher rate of subsequent fracture in bisphosphonate users with dementia. Among those with dementia, the rate of second fracture was 90% higher among bisphosphonate than denosumab users in Australia, but this was not significant when pooled with data from Taiwan. Furthermore, men using bisphosphonates rather than denosumab had a lower rate of death.

The 24% higher risk of subsequent fracture with bisphosphonate versus denosumab use was directionally consistent with the Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT), which reported that denosumab was associated with a 58% reduction in vertebral fractures compared to alendronate [28]. However, this RCT included individuals with osteoporosis and a history of vertebral rather than hip fractures. A meta-analysis of RCTs of people with osteoporosis has demonstrated that denosumab and alendronate are associated with a similar fracture incidence at 12 months, but denosumab is associated with lower fracture incidence at 24 months [5]. This suggests the benefits of denosumab may depend on follow-up duration, perhaps due to declining adherence or persistence over time. For example, alendronate and risedronate are administered orally, while denosumab is administered as a six-monthly subcutaneous injection. Oral bisphosphonates have gastrointestinal adverse events which may contribute to non-adherence. A study using data from the UK Clinical Practice Research Datalink found that post-menopausal women are more likely to cease oral bisphosphonates than denosumab treatment two years after treatment initiation

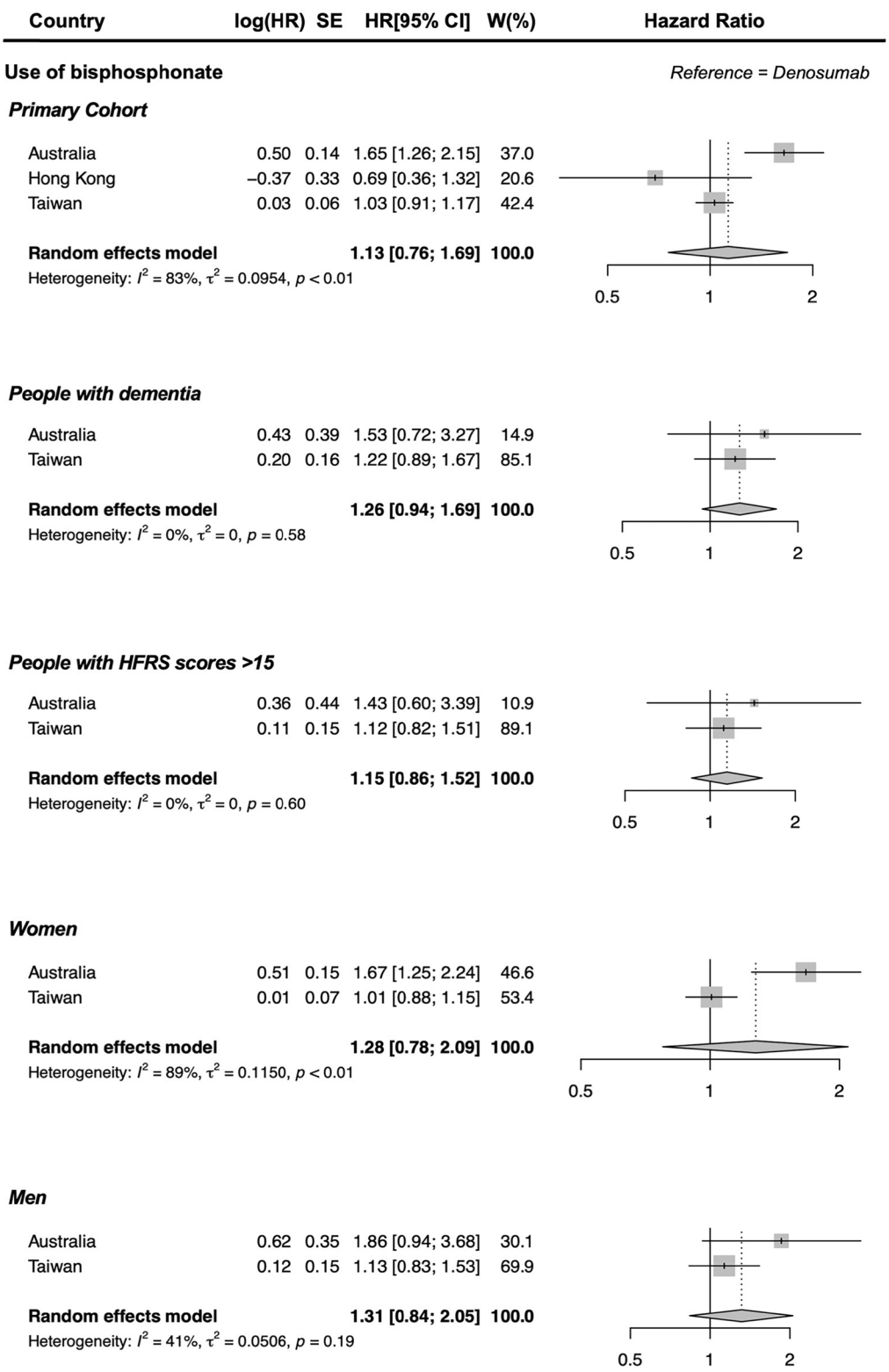

Fig. 3 **A** Forest Plots comparing bisphosphonates with denosumab in the risk of second hip fracture in the primary cohorts and in sub-populations. All-cause death treated as a competing event. HFRS: Hospital Frailty Risk Score. **B** Forest Plots comparing bisphosphonates with denosumab in the risk of any subsequent fracture in the primary cohorts and in sub-populations. All-cause death treated as a competing event. HFRS: Hospital Frailty Risk Score. **C** Forest Plots comparing bisphosphonates with denosumab in the risk of mortality in the primary cohorts and in sub-populations. HFRS: Hospital Frailty Risk Score

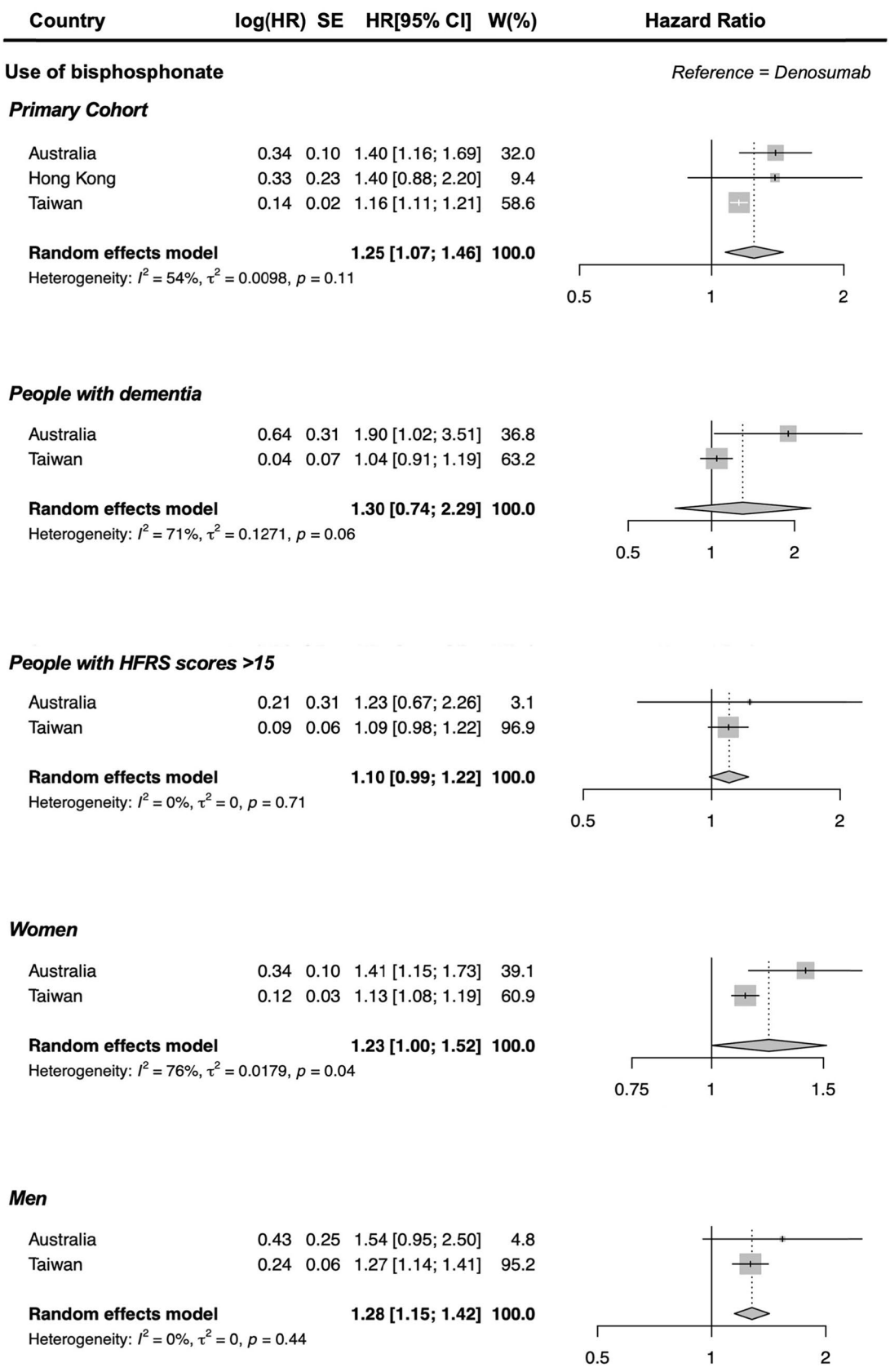

Fig. 3 (continued)

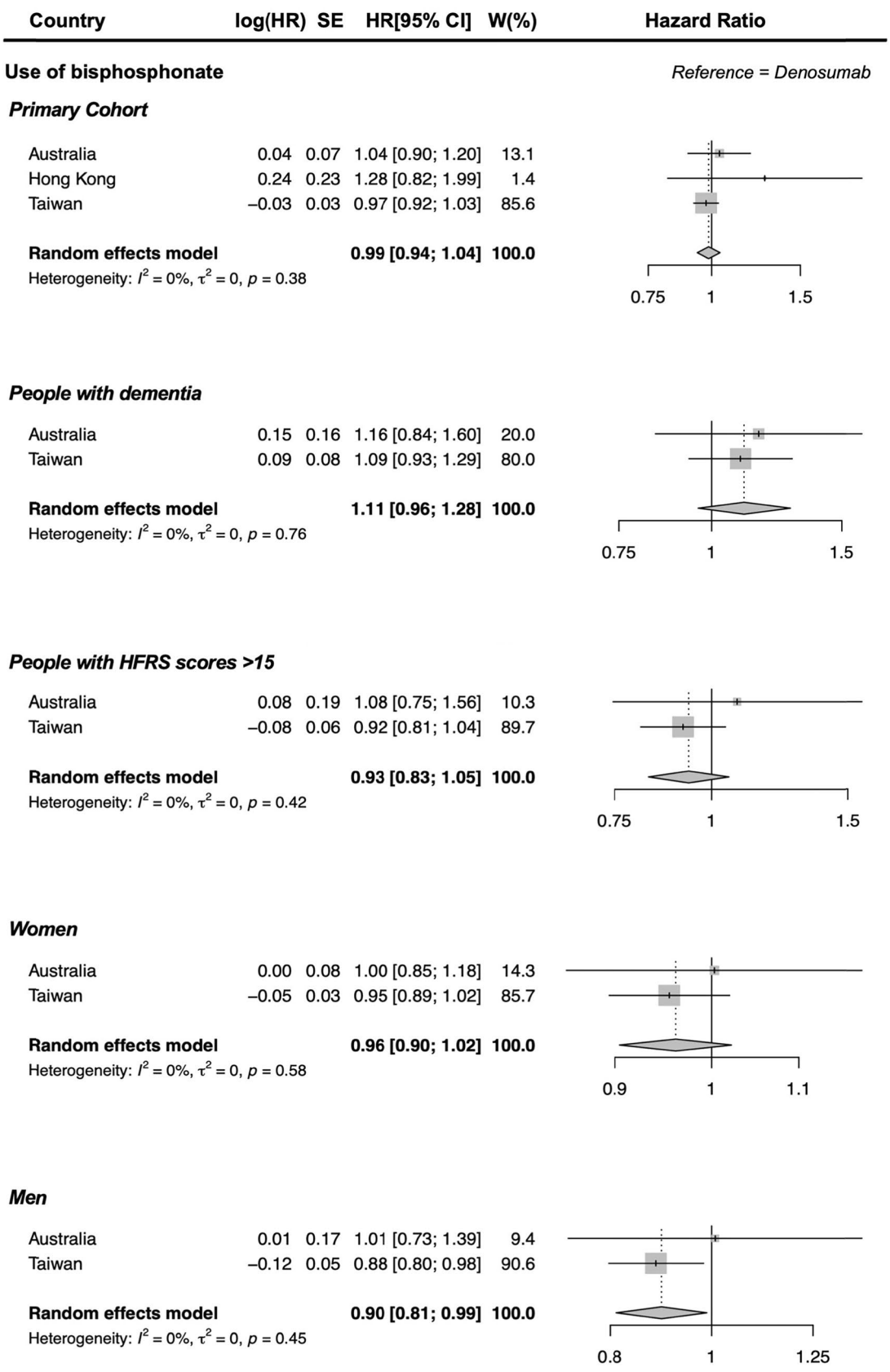

Fig. 3 (continued)

(72% vs. 36%) [19]. Despite different study populations, this may be similar among people with hip fracture.

In our meta-analysis, bisphosphonate and denosumab users had a similar mortality rate after the first hip fracture. However, bisphosphonates were associated with 10% lower mortality in men. It is possible that apparent survival benefits were attributable to confounding by comorbidity. Bisphosphonates are contraindicated in people with creatinine clearance < 30 mL/min1.73m^2 (alendronate, risedronate) or < 35 mL/min1.73m^2 (zoledronate). A higher proportion of men with CKD, which has a higher rate of mortality compared to those without CKD, may have been channeled to receive denosumab.

Differences in clinical practice guidelines and reimbursement criteria may explain why half of the people were dispensed bisphosphonates in Australia and Taiwan, and more than 90% in Hong Kong and the UK. Only a small sample of people were dispensed or prescribed denosumab in Hong Kong and the UK; this limited the opportunity to perform sub-analyses in these jurisdictions. In Australia, Hong Kong, and Taiwan, bisphosphonates and denosumab are both recommended as first-line osteoporotic therapies after hip fracture in clinical guidelines [1, 14, 15]. In Australia, the national PBS subsidizes both bisphosphonates and denosumab following a single minimal trauma fracture. However, the Hong Kong Hospital Authority only subsidizes denosumab when bisphosphonates are contraindicated or not tolerated, or have at least two fractures, one of which must be a fragility fracture [29]. In the UK, the National Institute for Health and Care Excellence recommends denosumab for secondary fracture prevention only in postmenopausal women not able to administer bisphosphonates, or in those with contraindications [30]. Furthermore, denosumab may have been prescribed during hospitalization and this was not captured in IMRD.

Across the jurisdictions, there were slight differences in the types of bisphosphonate available, which vary in potency [31]. Some less potent bisphosphonates were available in Taiwan and the UK, e.g., oral etidronate. This could lead to differences in associations observed between the jurisdictions. However, most bisphosphonates used in both Taiwan and the UK were the more potent nitrogen-containing bisphosphonates, i.e., oral alendronate, oral risedronate, and intravenous zoledronic acid [32–34], which were the only bisphosphonates available in Australia and Hong Kong.

Strengths and limitations

This was the first multi-database observational study to compare the outcomes of the two first-line anti-resorptive agents post hip fracture and stratified by people living with dementia and frailty. We utilized representative population databases across four jurisdictions. The study used a treatment decision design that reflects treatment choices made upon clinical review following hip fracture [35]. We used IPTW to control for confounders in each jurisdiction. This is considered a robust method for estimating treatment effects in observational studies [27]. Landmark methodology reduced immortal time bias. The validity of hip fracture ascertainment in the Hong Kong Hospital Authority data has been shown to be very good, with a positive predictive value (PPV) of 100% [24]. In Australia, the sensitivity of the principal diagnosis of hip fracture varies between 84 and 93% and the PPV between 68 and 90% [36].

Our study has several limitations. We analyzed clinical and administrative healthcare data not originally collected for research purposes. We used records of dementia diagnosis and dementia medication prescribing or dispensing to identify people with dementia, a common approach in observational studies in people with dementia and those evaluating dementia as an outcome [37, 38]. However, there was likely an under-capture of people with dementia, given dementia diagnoses are often under-recorded, and people might not initiate pharmacological treatment. This might limit the conclusions drawn in the subgroup analyses by dementia status. Furthermore, the HFRS to identify frailty was originally developed using hospital data, and has not been validated using the primary care data. Given that primary care data was utilized in the UK analyses, people might have been misclassified between frail vs. non-frail status. However, survival and subgroup analyses were not conducted given the lower number of denosumab users in the UK. Next, it is possible that clinicians' subjective assessment of patient longevity influenced their decision to prescribe or refrain from prescribing antiresorptive therapy. Our results may not be generalizable to individuals with relatively short-life expectancies, including those with very advanced frailty or dementia. People with severe cognitive impairment may have been less likely to receive oral bisphosphonates such as alendronate or risedronate because of the anticipated poor adherence, and more likely channeled to receive denosumab. Thus, the outcomes in the denosumab group may be less favorable than the bisphosphonate group. Our results cannot be generalized to all people with hip fracture because those receiving neither bisphosphonates nor denosumab were excluded. Our analyses did not consider the use of non-prescription medications which could influence bone mineral density and fracture risk, such as calcium and vitamin D. Similarly, we were unable to adjust our analyses for creatinine clearance or bone mineral density. While we utilized individual-level medication dispensing and prescribing data, we cannot confirm medication consumption. It is also possible that there was a difference in medication adherence between people with and without dementia. Given that the rate of bone loss is known to be higher during the menopausal period [39], the association

between antiresorptive medication use and risk of fracture may differ between perimenopausal women (aged 45–55) and older women (aged ≥ 65). However, since our study cohort was restricted to people aged ≥ 50 and most people who had their first recorded fracture were much older (more than 80% aged ≥ 70 across all jurisdictions; see Table 1), our results from the stratified analyses in women likely represent the association in older women only.

Conclusion

Bisphosphonate users had a higher rate of subsequent fracture than denosumab users, particularly in men. However, there was no difference in rates of second hip fracture or death. Among people with dementia, there was a non-significant trend toward a higher rate of subsequent fracture in bisphosphonate users. Men using bisphosphonates rather than denosumab had a lower rate of death, suggesting that sex may be an important consideration when selecting first-line anti-resorptive medication post hip fracture.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07676-x.

Author contribution JI, CWS, ECCL, TTM, WCYL, and JSB were responsible for the data acquisition. SW, SJHK, MTYL, CWS, MHCH, and TTM conducted the data analysis. JI, SW, ECCL, MHCH, WCYL, and JSB conceptualized and contributed to the design of the study. JI, SW, GSQT, MTYL, CWS, CLC, ECCL, MHCH, TTM, WCYL, ICKW, IDC, and JSB were involved in the manuscript write-up and review.

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Data availability The raw data of this study are not publicly available as they can only be accessed from a secured online workspace for approved users.

Declarations

Conflict of interest JI reports grants from AstraZeneca, Amgen, National Health and Medical Research Council, and National Breast Cancer Foundation, outside the submitted work. CLC received honorarium and research grants from Amgen Inc to conduct "Bone-Targeted Agents (BTAs) Awareness Campaign for Prostate Cancer Patients with Bone Metastasis" and "Validation of the osteoporosis prediction algorithm for Chinese using logistic regression and advanced machine learning approach." WCYL received research funding outside the submitted work from AIR@InnoHK administered by Innovation and Technology Commission. ICKW received research grants from Amgen Inc to conduct study on "Global Epidemiology of Hip Fracture" and "Bone-Targeting Agents Among Asian Patients with Bone Metastases from Solid Tumors." JSB is supported by a National Health and Medical Research Council (NHMRC) Boosting Dementia Research Leadership Fellowship and has received grant funding or consulting funds from the NHMRC, Victorian Government Department of Health and Human Services, Dementia Australia Research Foundation, Yulgilbar Foundation, Aged Care Quality and Safety Commission, Dementia Centre for Research Collaboration, Pharmaceutical Society of Australia, Society of Hospital Pharmacists of Australia, GlaxoSmithKline Supported Studies Programme, Amgen, and several aged care provider organizations unrelated to this work. All grants and consulting funds were paid to the employing institution. SW, GSQT, SJHK, MTYL, CWS, ECCL, MHCH, TTM, and IDC declare that they have no conflict of interest.

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