Table 1. Baseline characteristics of included studies

Author (Year of publication)	Study design (study period)	Study duration	Source of data (country)	Study population	Exposed group vs comparison group	Outcome reported	Method to ascertain fracture	Important exclusion for confounding	Sample size	Mean follow-up time	% Female	Mean age (SD)
Norby FL, et al. (2017)	A retrospective cohort study	5 years (1 January 2010 to 31 December 2014)	Healthcare claims data from the Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database (United States)	Non-valvular AF	Rivaroxaban vs warfarin (new users)	A composite of hip or pelvic fracture	ICD-9-CM codes	None relating to fracture (usual AF exclusions)	77991 (32495 in rivaroxaban group and 45496 in warfarin group)	NR	38.7% in rivaroxaban group and 40.1% in warfarin group	69.3 (12.2) in rivaroxaban group and 71.1 (12.5) in warfarin group
Binding C, et al. (2019)	A retrospective cohort study	4.5 years (January 1, 2013, and June 30, 2017)	1. Danish National Patient Register 2. The National Prescrtipion Registry 3. Danish Civil	Non-valvular AF	NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) vs VKA	1) any fractures; 2) hospital admission with fractures; 3) hip fracture; 4) initiation of	ICD-10	Patients who received osteoporotic medications prior to study inclusion	37350 (25182 in NOAC group and 12168 in VKA group)	NR	44.1% in DOAC group and 38.2% in VKA group	Median age (IRQ): 73 yrs (67–81) in NOACs and 72 yrs (65–79) in VKA

Author (Year of publication)	Study design (study period)	Study duration	Source of data (country)	Study population	Exposed group vs comparison group	Outcome reported	Method to ascertain fracture	Important exclusion for confounding	Sample size	Mean follow-up time	% Female	Mean age (SD)
			Registration System (Denmark)			osteoporosis medication; and 5) a combined endpoint of any fracture or initiation of osteoporosis medication						
Lutsey PL, et al. (2019)	A retrospective cohort study	5 years, 9 months (1 January 2010 to 30 September 2015)	The MarketScan Commercial Claims and Encounters and MarketScan Medicare Supplemental and Coordination of Benefits databases (United States)	Non-valvular AF	NOACs (dabigatran, rivaroxaban, apixaban) vs warfarin (new user)	1) hip fractures; 2) fractures requiring hospitalization, and 3) all clinical fractures	ICD-9-CM codes	Patients with fracutres within 90 days of inclusion	111652 (55826 in NOAC group and 55826 in warfarin)* after matching	16.9 (SD 13.7) months	38% (34.9% in dabigatran, 38.1% in rivaroxaban, 39.9% in apixaban and 38.8% in warfarin)	68.9 (12.5) years [67.0 (12.4) in dabigatran, 67.7 (12.3) in rivaroxaban, 69.1 (12.6) in apixaban and 70.2 (12.3) in warfarin]
Huang HK, et al. (2020)	A retrospective cohort study	6 years (2012 to 2017)	Taiwan's National Health Insurance Research Database	Newly diagnosed AF age ≥ 20	Dabigatran, rivaroxaban, apixaban vs	Any new fracture of the hip , vertebrae, or humerus,	ICD-9-CM codes		19414 (9707 in NOACs and 9707 in warfarin)	Median =2.4 years	40.8% in NOACs and 41.1% in warfarin	72.4 (10.7) in NOACs and 71.3 (11.5) in warfarin

Author (Year of publication)	Study design (study period)	Study duration	Source of data (country)	Study population	Exposed group vs comparison group	Outcome reported	Method to ascertain fracture	Important exclusion for confounding	Sample size	Mean follow-up time	% Female	Mean age (SD)
			(NHIRD) (Taiwan)		warfarin (new user)	forearm, or wrist			*after matching			
Lau WC, et al. (2020)	A retrospective cohort study	9 years (1 January 2010 until 31 December 2018)	The Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (Hong Kong)	Non-valvular AF	NOAC (dabigatran, rivaroxaban, apixaban) vs warfarin (new user)	A composite of hip fracture and vertebral fractures	ICD-9-CM codes	Patients with bone tumours, epilepsy or history of seizure (anytime prior to index date), or baseline use of (within 90 days): hormone therapy	23,515 (13,974 in NOAC group vs 9541 in warfarin group)	Median= 423 days (IQR; 92 to 1001 days)	48.0% (49.9% in NOAC and 45.2% in warfarin)	74.4 (10.8)

Abbreviations: AF=atrial fibrillation; ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; NR=not reported; NOAC=non-vitamin K antagonist oral anticoagulant; VKA=vitamin K antagonist; IRQ=interquartile range; SD=standard deviation; ICD-10= International Classification of Diseases, Tenth Revision

Table 2. Meta-analysis results according to secondary endpoints overall and for each individual NOACs

Outcomes	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity test			
				X^2	P-value	I^2-index	τ^2
Hip fractures							
Overall NOACs	3[14,18,19]	0.89 (0.80-0.99)	0.036	0.32	0.851	0.0%	0.00
Dabigatran	2[14,19]	0.99 (0.85-1.15)	0.883	0.02	0.898	0.0%	0.0
Rivaroxaban	2[14,19]	0.89 (0.76-1.05)	0.156	0.00	1.000	0.0%	0.0
Apixaban	2[14,19]	0.62 (0.45-0.86)	0.004	0.44	0.506	0.0%	0.0
Vertebral fractures							
Overall NOACs	1[19]	0.75 (0.65-0.86)	<0.001	NA	NA	NA	NA
Dabigatran	1[19]	0.81 (0.68-0.95)	0.011	NA	NA	NA	NA
Rivaroxaban	1[19]	0.73 (0.62-0.85)	<0.001	NA	NA	NA	NA
Apixaban	1[19]	0.6 (0.41-0.88)	0.009	NA	NA	NA	NA
Hip and vertebral fractures							
Overall NOACs	-	-	-	-	-	-	-
Dabigatran	1[20]	0.65 (0.49-0.86)	0.003	NA	NA	NA	NA
Rivaroxaban	1[20]	0.52 (0.37-0.73)	<0.001	NA	NA	NA	NA
Apixaban	1[20]	0.62 (0.41-0.94)	0.025	NA	NA	NA	NA
Hip or pelvic fractures							
Overall NOACs	-	-	-	-	-	-	-
Dabigatran	-	-	-	-	-	-	-
Rivaroxaban	1[29]	0.83 (0.70-0.99)	0.04	NA	NA	NA	NA
Apixaban	-	-	-	-	-	-	-
Humerus/forearm/wrist fractures							
Overall NOACs	1[19]	0.88 (0.73-1.06)	0.190	NA	NA	NA	NA
Dabigatran	1[19]	0.96 (0.76-1.20)	0.694	NA	NA	NA	NA
Rivaroxaban	1[19]	0.78 (0.62-0.98)	0.030	NA	NA	NA	NA
Apixaban	1[19]	1.04 (0.63-1.74)	0.869	NA	NA	NA	NA
A composite of hip, vertebrae, or humerus, forearm, or wrist fractures							
Overall NOACs	1[19]	0.84 (0.77-0.93)	<0.001	NA	NA	NA	NA
Dabigatran	1[19]	0.88 (0.78-0.99)	0.027	NA	NA	NA	NA
Rivaroxaban	1[19]	0.81 (0.72-0.90)	<0.001	NA	NA	NA	NA
Apixaban	1[19]	0.67 (0.52-0.87)	0.003	NA	NA	NA	NA

Hospital admission due to fractures							
Overall NOACs	2[14,18]	0.87 (0.80-0.94)	0.001	0.06	0.807	0.0%	0.00
Dabigatran	1[14]	0.88 (0.78-1.00)	0.06	NA	NA	NA	NA
Rivaroxaban	1[14]	0.80 (0.69-0.93)	0.003	NA	NA	NA	NA
Apixaban	1[14]	0.60 (0.47-0.78)	<0.001	NA	NA	NA	NA

Abbreviations: NOACs= non-vitamin K antagonist oral anticoagulants; CI=confident interval; NA=not applicable