SUPPLEMENT

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Supplement 1: Search syntax

Search from January 1st 2009 until July 10th 2022, PubMed:

(dose*[Title/Abstract] OR dosa*[Title/Abstract] OR dosi*[Title/Abstract]) AND

(low[Title/Abstract] OR lower*[Title/Abstract] OR adjust*[Title/Abstract] OR adapt*[Title/Abstract] OR alter*[Title/Abstract] OR modif*[Title/Abstract] OR regulat*[Title/Abstract] OR tailor*[Title/Abstract] OR reduc*[Title/Abstract] OR underdos*[Title/Abstract] OR *recommend*[Title/Abstract] OR inappropria*[Title/Abstract] OR appropria*[Title/Abstract] OR incorrect*[Title/Abstract] OR correct*[Title/Abstract] OR incongrue*[Title/Abstract] OR congrue*[Title/Abstract] OR discord*[Title/Abstract] OR concord*[Title/Abstract] OR offlabel[Title/Abstract] OR off-label[Title/Abstract] OR (off[Title/Abstract] AND label[Title/Abstract]) OR "Off-Label Use"[Mesh]) AND

(dabigatran[Title/Abstract] OR "dabigatran"[Mesh] OR pradaxa[Title/Abstract] OR rivaroxaban[Title/Abstract] OR "rivaroxaban"[Mesh] OR xarelto[Title/Abstract] OR apixaban[Title/Abstract] OR eliquis[Title/Abstract] OR edoxaban[Title/Abstract] OR lixiana[Title/Abstract] OR NOAC*[Title/Abstract] OR DOAC*[Title/Abstract] OR ((anticoagul*[Title/Abstract] OR anti-coagul*[Title/Abstract] OR "Anticoagulants"[Mesh]) AND (novel[Title/Abstract] OR new[Title/Abstract] OR direct[Title/Abstract])) OR (non[Title/Abstract] AND ((*vitamin*[Title/Abstract] AND *antagonist*[Title/Abstract]) OR VKA[Title/Abstract])))

Search from January 1st 2009 until July 10th 2022, EMBASE:

(dose*:ti,ab OR dosa*:ti,ab OR dosi*:ti,ab) AND

(low:ti,ab OR lower*:ti,ab OR adjust*:ti,ab OR adapt*:ti,ab OR alter*:ti,ab OR modif*:ti,ab OR regulat*:ti,ab OR tailor*:ti,ab OR reduc*:ti,ab OR underdos*:ti,ab OR recommend*:ti,ab OR non-recommend*ti,ab OR nonrecommend*ti:ab OR inappropria*:ti,ab OR appropria*:ti,ab OR incorrect*:ti,ab OR correct*:ti,ab OR incongrue*:ti,ab OR congrue*:ti,ab OR discord*:ti,ab OR concord*:ti,ab OR offlabel:ti,ab OR 'off-label':ti,ab OR 'off label':ti,ab OR 'off label drug use'/exp) AND

(dabigatran:ti,ab OR 'dabigatran'/exp OR 'dabigatran etexilate'/exp OR pradaxa:ti,ab OR rivaroxaban:ti,ab OR 'rivaroxaban'/exp OR xarelto:ti,ab OR apixaban:ti,ab OR 'apixaban'/exp OR eliquis:ti,ab OR edoxaban:ti,ab OR 'edoxaban'/exp OR lixiana:ti,ab OR noac*:ti,ab OR DOAC*:ti,ab OR

((anticoagul*:ti,ab OR 'anti-coagul*':ti,ab OR 'anticoagulant agent'/exp) AND (novel:ti,ab OR new:ti,ab OR direct:ti,ab) OR (non*:ti,ab AND ((vitamin*:ti,ab AND antagonist*:ti,ab) OR (VKA*:ti,ab))))) AND

'article'/it AND [embase]/lim AND [1-1-2009]/sd NOT [10-07-2022]/sd

Supplement 2: Risk of bias assessment items based on the Newcastle-Ottawa quality assessment Scale for cohort studies (NOS)

Note: A study can be awarded a maximum of one star (i.e. *) for each numbered item within the Selection, Outcome and Missing data categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
    a. truly representative of the average AF patient without a mechanical heart valve and/or severe mitral valve stenosis who is treated with a NOAC for stroke prevention in the community *
    b. somewhat representative of the average AF patient without a mechanical heart valve and/or severe mitral valve stenosis who is treated with a NOAC for stroke prevention in the community *
    c. selected group of users eg nurses, volunteers
    d. no description of the derivation of the cohort
2) Selection of the non exposed cohort
    a. drawn from the same community as the exposed cohort *
    b. drawn form a different source
    c. no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a. secure record (eg surgical records) *
    b. structured interview *
    c. written self report
    d. no description

4) Demonstration that outcome of interest was not present at start of study

    a. yes *

    b. no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

    a. study controls for sex and age *

    b. study controls for any additional factor *

Outcome

1) Assessment of outcome

    a. independent blind assessment *

    b. record linkage *

    c. self report

    d. no description

2) Was follow-up long enough for outcomes to occur

    a. yes (i.e. >90 days) *

    b. no

    c. no follow-up period was reported

3) Adequacy of follow-up of cohorts

    a. complete follow up – all subjects accounted for *

    b. subjects lost to follow up unlikely to introduce bias – small number lost - >90% follow up, or description provided of those lost *

    c. follow up rate <90% and no description of those lost

    d. no statement

Missing data

1) Handling missing data

    a. multiple imputation *

    b. no multiple imputation

    c. not reported

Supplement 3: Extracted study and patient characteristics

Study characteristics	Data source (i.e. electronic health record, prospective registry)
	Country
	Setting (i.e. general care, specialist care, both)
	Time frame (i.e. inclusion period)
	NOAC (i.e. dabigatran, rivaroxaban, apixaban, edoxaban)
	Guideline used to determine whether a non-reduced or a reduced NOAC dose was indicated (i.e. SPC, FDA, ESC, EHRA, landmark NOAC trial(s), other guideline, not reported)
	Number of included patients with AF who use a NOAC
	Duration of follow-up in months
Patient characteristics	Male sex in percentage
	Age in years in mean (or median)
	Weight in kilograms in mean (or median)
	Body mass index in mean (or median)
	eGFR (or CrCl) in mean (or median)
	Patients with an eGFR below 50 in percentage
	Patients with hypertension in percentage
	Patients with a history of (ischemic) stroke (and TIA and/or thromboembolism) in percentage (including definition)
	Patients with a history of hemorrhagic stroke in percentage
	Patients with (a history of) coronary heart disease in percentage (including definition)
	Patients with (a history of) (peripheral) vascular disease in percentage
	Patients with heart failure in percentage
	Patients with (a history of) other cardiovascular disease in percentage (including definition)
	Patients with diabetes mellitus in percentage
	Patients with chronic kidney disease in percentage (including definition)
	Patients using concomitant drugs that interact with NOACs in percentage (including the type of drug)

AF = atrial fibrillation; CrCl = creatinine clearance; eGFR = estimated Glomerular Filtration Rate; EHRA = European Heart Rhythm Association; ESC= European Society of Cardiology; FDA = Food and Drugs Administration; NOAC = non-vitamin K antagonist oral anticoagulant; SPC = Summary of Product Characteristics; VKA = vitamin K antagonist.

Supplement 4: Overview of the excluded studies based on full-text screening, including reason for exclusion*

Author	Year	Reference	Reason for exclusion
Lafon	2018	(1)	No full-text available
Aguilar	2021	(2)	Highly selected group of patients or data on patients with non-valvular atrial fibrillation cannot be extracted
Alcusky	2018	(3)	
Alghadeer	2017	(4)	
Alnsasra	2018	(5)	
Altay	2017	(6)	
Asahina	2020	(7)	
Chaudhry	2021	(8)	
de Almeida	2020	(9)	
Eschler	2021	(10)	
Frol	2020	(11)	
George	2019	(12)	
Gurevitz	2021	(13)	
Haque	2021	(14)	
Inohara	2020	(15)	
Jackevicius	2021	(16)	
Khan	2016	(17)	
Kim	2019	(18)	
Kwon	2016	(19)	
Lafon	2017	(20)	
Mitrovic	2017	(21)	
Nahornyj	2020	(22)	
Paciaroni	2019	(23)	
Rutherford	2021	(24)	
Shinoda	2018	(25)	
Shinohara	2019	(26)	
Shinohara	2019	(27)	
Szeto	2021	(28)	

Ting	2020	(29)	
Tran	2017	(30)	
Whitworth	2017	(31)	
Akagi	2019	(32)	Study does not report off-label reduced dosing compared to on-label non-reduced dosing.
Akao	2014	(33)	
Amarenco	2018	(34)	
Anouassi	2021	(35)	
Armbruster	2014	(36)	
Ashraf	2021	(37)	
Blin	2019	(38)	
Bouget	2020	(39)	
Camm	2020	(40)	
Chan	2020	(41)	
Chen	2021	(42)	
Cheng	2019	(43)	
Cho	2019	(44)	
De Caterina	2021	(45)	
Ebrahimi	2017	(46)	
Feng	2021	(47)	
Fernandez	2021	(48)	
Forslund	2018	(49)	
Gabitova	2019	(50)	
Godino	2020	(51)	
Hecker	2016	(52)	
Helmert	2017	(53)	
Hussain	2012	(54)	
Inoue	2019	(55)	
Isaacs	2013	(56)	
Isaacs	2016	(57)	
Jang	2019	(58)	
Jansson	2019	(59)	
Kohsaka	2020	(60)	

Kotalczyk	2021	(61)	
Larsen	2013	(62)	
Lee	2015	(63)	
Li	2017	(64)	
Marzona	2021	(65)	
Muniz Lobato	2018	(66)	
Navarro-Almenzar	2019	(67)	
Nielsen	2017	(68)	
Ogawa	2014	(69)	
Perreault	2020	(70)	
Qian	2021	(71)	
Raccah	2021	(72)	
Rahme	2021	(73)	
Ruiz-Ortiz	2020	(74)	
Russo	2015	(75)	
Sato	2018	(76)	
Shrestha	2018	(77)	
Staerk	2018	(78)	
Sugrue	2021	(79)	
Wattanaruengchai	2020	(80)	
Yu	2020	(81)	
Bando	2018	(82)	
Bang	2020	(83)	
Barra	2016	(84)	
Bastida	2017	(85)	
Brook	2020	(86)	
Chao	2021	(87)	
Eschler	2020	(88)	
Gustafson	2019	(89)	
Ionin	2021	(90)	
Kartas	2019	(91)	
Kilickiran Avci	2016	(92)	

Kimmons	2014	(93)	Study does not report association between off-label reduced dosing and outcome(s).
Larock	2014	(94)	
Lee	2020	(95)	
Lodzinksi	2020	(96)	
Masunaga	2018	(97)	
Miyazaki	2022	(98)	
Pisters	2017	(99)	
Sato	2018	(100)	
Sato	2020	(101)	
Suwa	2019	(102)	
Tedders	2013	(103)	
Tellor	2015	(104)	
Tran	2014	(105)	
Umei	2017	(106)	
Vinding	2019	(107)	
Xing	2019	(108)	
Yiginer	2017	(109)	
Zeymer	2020	(110)	
Abe	2021	(111)	Other
Steinberg	2016	(112)	
Ueda	2020	(113)	

* In case there were several reasons to exclude a study, the reason mentioned first in the table above is reported.

Supplement 5: Detailed overview of all extracted study and patient characteristics

Last date of inclusion	First date of inclusion	Setting (i.e. general care, specialist care, both)	Country	Data source	Year	Study characteristics	Author*
31-12-2017	01-01-2011	Both	Israel	EHR	2019		**Arbel** (114)
30-06-2016	01-11-2012	Both	Japan	PR	2021		**Atarashi** (115)
31-12-2016	01-10-2010	Both	USA	EHR	2020		**Briasoulis – dabigatran/rivaroxaban** (116)
31-12-2016	01-10-2010	Both	USA	EHR	2020		**Briasoulis – dabigatran** (116)
31-12-2016	01-10-2010	Both	USA	EHR	2020		**Briasoulis – rivaroxaban** (116)
31-12-2016	01-07-2015	SC	Kora	EHR	2020		**Cho – rivaroxaban/apixaban** (117)
31-12-2016	01-07-2015	SC	Korea	EHR	2020		**Cho – rivaroxaban** (117)
31-12-2016	01-07-2015	SC	Korea	EHR	2020		**Cho – apixaban** (117)
n.r.	01-08-2015	Both	Multi-national [1]	PR	2020		**de Groot** (118)
30-06-2014	01-04-2012	Both	Japan	PR	2019		**Ikeda** (119)
30-11-2013	12-12-2011	Both	Japan	PR	2019		**Inoue – 2019** (120)
31-08-2014	01-09-2013	Both	Japan	PR	2020		**Inoue – 2020** (121)
30-11-2017	01-06-2011	SC	Japan	PR	2020		**Kobayashi** (122)
31-12-2013	01-01-2012	SC	Korea	EHR	2017		**Lee – 2017** (123)
31-12-2016	01-01-2014	Both	Korea	EHR	2019		**Lee – 2019** (124)
31-12-2017	01-01-2015	Both	Korea	EHR	2021		**Lee – 2021** (125)
31-12-2015	01-09-2013	Both	Japan	PR	2019		**Murata** (126)
30-11-2017	01-06-2011	Both	Japan	PR	2020		**Ohno** (127)
31-12-2017	01-11-2013	Both	Israel	EHR	2020		**Salameh** (128)
31-07-2016	01-02-2013	Both	USA	PR	2018		**Steinberg** (129)
30-06-2016	01-01-2013	SC	USA	EHR	2017		**Tellor** (130)
31-07-2017	01-05-2012	SC	Japan	PR	2019		**Yagi** (131)
30-09-2015	01-10-2010	Both	USA	EHR	2017		**Yao – dabigatran** (132)
30-09-2015	01-10-2010	Both	USA	EHR	2017		**Yao – rivaroxaban** (132)
30-09-2015	01-10-2010	Both	USA	EHR	2017		**Yao – apixaban** (132)

eGFR <50 (%)	eGFR (mean)	Body mass index (mean)	Weight in kg (mean)	Age in years (mean)	Male sex (%)	Patient characteristics	Duration of follow-up (months)	NOAC-users (n)	Guideline used	NOAC
n.r.	71.5	30.2	n.r.	75.5	48.0		23	8,425	SPC	D/R/A
n.r.	n.r.	n.r.	62.7	71.6	67.7		n.r.	6,806	J-ROCKET-AF	R
48.8 [11]	n.r.	n.r.	n.r.	n.r.	50.5		12.5	27,747	D: FDA R: other [2]	D/R
53.0 [11]	n.r.	n.r.	n.r.	n.r.	50.6		14.8	8,035	FDA	D
47.0 [11]	n.r.	n.r.	n.r.	n.r.	50.2		11.6	19,712	Other [2]	R
n.r.	69.6 ◦	25.3	n.r.	70.3	54.4		15.0 ǂ	16,568	R: ROCKET-AF A: ARISTOTLE	R/A
n.r.	72.7 ◦	25.5	n.r.	69.8	59.4		15.0 ǂ	9,639	ROCKET-AF	R
n.r.	65.4 ◦	25.0	n.r.	71.0	47.4		15.0 ǂ	6,929	ARISTOTLE	A
n.r.	74.3 ◦	28.1	81.0	73.6	56.8		11.6 ǂ	13,092	SPC	E
0	77.7 ◦	24.7	64.9	70.4	68.3		±12	6,521 [10]	J-ROCKET-AF	R
18	72.9 ◦	24.0	62.7	70.9	66.9		15.1 ǂ	6,443	Other [3]	D
31.4	62.2 ◦	n.r.	59.5	74.5	58.9		17.4	6,294	ARISTOTLE	A
n.r.	80.3 ◦	n.r.	65.8	67.2	73.6		13.4	1,245	ARISTOTLE + other [4]	D/R/A/E
n.r.	66.1 ◦ ǂ	n.r.	n.r.	74.0	62.2		±12	844	Other [5]	D
n.r.	82.5 ◦	24.8	64.9	69.8 ǂ	57.4		16.8 ǂ	13,594	ROCKET-AF	R
7.6	77.1	24.6	63.6	72.6	56		24ǂǂ	8,512	ESC	A
n.r.	70.5 ◦	24.1	63.8	71.7	71.5		39.3 ǂ	1,658	ARISTOTLE + other [6]	D/R/A/E
n.r.	65.4	23.7	60.9	71.6	63.6		13.4	2,195	ARISTOTLE + SPC + other [7]	D/R/A/E
n.r.	63.8	n.r.	78.1	78.7	48.3		15.3	27,765	SPC	A
n.r.	81.7 ◦ ǂ	n.r.	n.r.	71 ǂ	58.7		12.0 ǂ	7,925	FDA	D/R/A/E
n.r.	42 ◦	n.r.	86.9	75.1	48.7		16.3	707	FDA	A
15.7	64.1	n.r.	67.1	69.1	78		10.8 ǂ	661	J-ROCKET-AF	R
13.6	71.6	n.r.	n.r.	68.3	61.7		4.0 ǂ	4,653	Other [8]	D
0	76.4	n.r.	n.r.	69.6	59.9		4.0 ǂ	5,399	FDA	R
12.6	71.1	n.r.	n.r.	72.4	50.6		4.0 ǂ	3,340	Other [9]	A

Concomitant PI (%)	Chronic kidney disease (%) – definition	Diabetes mellitus (%)	(History of) other cardiovascular disease (%) – definition	Heart failure (%)	(History of) (peripheral) vascular disease (%)	(History of) coronary heart disease (%) – definition	History of hemorrhagic stroke (%)	History of (ischemic) stroke (and TIA and/or thromboembolism) (%) – definition	Hypertension (%)
42.3	18.0 – [21]	59.8	n.r.	26.9	16.6	n.r. – n.a.	n.r.	31.4 – [12]	95.4
9.4	n.r. – n.a.	24.7	n.r.	26.5	n.r.	4.2 – MI	1.9	20.2 – [13]	71.2
26.6	24.9 – [22]	48.0	n.r.	29.9	n.r.	6.5 – MI	0.9	24.5 – [12]	93.2
27.5	23.3 – [22]	49.2	n.r.	34.4	n.r.	5.7 – MI	0.7	24.8 – [12]	93.9
26.2	25.6 – [22]	48.8	n.r.	28.0	n.r.	6.8 – MI	1.0	24.3 – [12]	92.9
9.1 [29]	2.7 – [23]	46.6	n.r.	19.1	11.4	n.r. – n.a.	1.1	19.9 – [14]	87.6
8.9 [29]	1.8 – [23]	47.0	n.r.	18.7	11.0	n.r. – n.a.	0.9	18.6 – [14]	88.4
9.5 [29]	3.9 – [23]	46.1	n.r.	19.6	11.8	n.r. – n.a.	1.5	21.8 – [14]	86.4
n.r.	n.r. – n.a.	22.0	n.r.	5.9	3.3 [18]	4.3 – MI	0.5	5.9 – [13]	77.1
13.7	0 – [24]	23.3	3.2 – [19]	21.0	n.r.	n.r. – n.a.	n.r.	20.5 – [15]	74.5
13.8	n.r. – n.a.	20.4	n.r.	18.2	n.r.	n.r. – n.a.	n.r.	20.2 – [12]	66.7
18.8	41.5 – [25]	55	n.r.	30.4	n.r.	n.r. – n.a.	n.r.	17.5 – [15]	61.2
21.9 [30]	n.r. – n.a.	28.4	n.r.	17.4	n.r.	18.5 – CAD	n.r.	16.9 – [12]	71.2
n.r.	n.r. – n.a.	22.2	n.r.	9.1	n.r.	5.8 – MI	n.r.	49.8 – [16]	65.2
n.r.	n.r. – n.a.	22.4	n.r.	30.4	17.7 [18]	2.8 – MI	n.r.	n.r. – n.a.	72.2
34.3	n.r. – n.a.	27.8	n.r.	46.1	26.8 [18]	6.1 – MI	n.r.	29.2 – [12]	85.5
12.7	n.r. – n.a.	21.6	n.r.	19.1	11.7	n.r. – n.a.	n.r.	10.1 – [16]	69.4
21.5	39.2 – [26]	26.1	n.r.	32.5	7.2	19.9 – CAD	n.r.	20.3 – [12]	73.3
48.9	2.8 – [27]	46.4	n.r.	32.6	12.5	31.9 – MI	n.r.	24.9 – [12]	90.1
25.7 [30]	n.r. – n.a.	n.r.	n.r.	n.r.	n.r.	n.r. – n.a.	n.r.	11.1 – [16]	n.r.
53.3	5- [28]	n.r.	n.r.	n.r.	n.r.	n.r. – n.a.	n.r.	n.r. – n.a.	n.r.
11.0	n.r. – n.a.	16	5.0 – [20]	17.0	n.r.	n.r. – n.a.	n.r.	6.0 – [15]	54
6.4	n.r. – n.a.	41.8	n.r.	27.9	25.2	n.r. – n.a.	1.0	14.0 – [17]	88.7
7.4	n.r. – n.a.	39.3	n.r.	26.5	26.7	n.r. – n.a.	0.8	13.1 – [17]	88.1
7.5	n.r. – n.a.	39.7	n.r.	31.8	29.1	n.r. – n.a.	1.6	14.7 – [17]	90.8

OLRD of patients with an indication for an on-label non-reduced NOAC dose (%)	On-label non-reduced dose (n)	Off-label reduced dose (n)	Other concomitant drug that interacts with NOACs (%) – type of drug	Concomitant P-gp inhibitor (%)	Concomitant NSAID (%)
Off-label reduced and on-label non-reduced NOAC dose					
39.0	5,140	3,285	n.r. – n.a.	n.r.	43.3
30.2	3,717	1,609	n.r. – n.a.	n.r.	n.r.
19.2	14,962	3,564	18.2 – warfarin	19.6	51.0
15.3	5,621	1,013	24.4 – warfarin	22.5	50.9
21.5	9,341	2,551	15.7 – warfarin	18.4	51.0
51.6	8,019	8,549	4.9 – ADP-2 inhibitor	n.r.	n.r.
50.6	4,760	4,879	4.5 – ADP-2 inhibitor	n.r.	n.r.
53.0	3,259	3,670	5.6 – ADP-2 inhibitor	n.r.	n.r.
11.2	8,872	1,114	n.r. – n.a.	n.r.	n.r.
35.8	4,185	2,336	n.r. – n.a.	n.r.	n.r.
49.7	1,196	1,181	n.r. – n.a.	3.3	n.r.
22.5	3,241	941	n.r. – n.a.	n.r.	n.r.
27.1	907	338	n.r. – n.a.	n.r.	n.r.
38.4	294	183	n.r. – n.a.	n.r.	n.r.
42.6	7,798	5,796	n.r. – n.a.	n.r.	n.r.
40.8	4,194	2,890	n.r. – n.a.	n.r.	n.r.
33.1	746	369	n.r. – n.a.	n.r.	2.0
27.1	907	338	n.r. – n.a.	n.r.	n.r.
42.9	13,141	9,885	n.r. – n.a.	n.r.	n.r.
10.3	6,376	734	n.r. – n.a.	n.r.	n.r.
17.0	477	98	n.r. – n.a.	n.r.	n.r.
23.1	409	123	n.r. – n.a.	n.r.	n.r.
8.9	4,241	412	n.r. – n.a.	n.r.	4.8
9.6	4,881	518	n.r. – n.a.	n.r.	4.8
16.5	2,790	550	n.r. – n.a.	n.r.	5.0

A = apixaban; ADP = adenosine diphosphate; AF = atrial fibrillation; b.i.d. = bis in die (= twice a day); CAD = coronary artery disease; CrCl = creatinine clearance; D = dabigatran; E = edoxaban; eGFR = estimated Glomerular Filtration Rate; EHR = electronic health record; ESC= European Society of Cardiology; FDA = Food and Drugs Administration; GI = gastrointestinal; ICD = International Classification of Diseases and Related Health Problems; i.e. = id est (= that is); kg = kilogram; MI = myocardial infarction; n.a. = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; n.r. = not reported; NSAID = non-steroidal anti-inflammatory drug; o.d. = omnie die (= once a day); OLRD = off-label reduced dosing; P-gp = P-glycoprotein; PI = platelet inhibitor; PR = prospective registry; R = rivaroxaban; SC = specialist care; SPC = Summary of Product Characteristics; TIA = transient ischemic attack; USA = United Stated of America; VKA = vitamin K antagonist.

[1] Austria, Belgium, Germany, Ireland, Italy, Portugal, Spain, Switzerland, The Netherlands, United Kingdom; [2] FDA or concomitant use of a dual P-gp-Cyp3A4 inhibitor (including ketoconazole, fluconazole, itraconazole, cobicistat, conivaptan, indinavir, voriconazole, posaconazole, nefzadone HCL, ritonavir, saquinavir, telithromycin); [3] age ≥70 years, CrCl of 30-50mL/min, prior GI-bleeding, or concomitant use of oral P-gp inhibitors; [4] D: elderly >70 years, CrCl 30-50mL/min, concomitant use of P-gp inhibitors, history of GI-bleeding, R: CrCl 15-49mL/min, A: ARISTOTLE, E: body weight ≤60kg, CrCl 15-50mL/min, concomitant use of P-gp inhibitors; [5] old age (≥75 years old), renal dysfunction (glomerular filtration rate <50mL/min), or low body weight (<50kg); [6] D 110mg b.i.d.: CrCl 30-50mL/min, age ≥70 years and a prior history of bleeding, R 10mg

o.d.: CrCl 15-50mL/min, A 2.5mg b.i.d.: ARISTOTLE, E 30mg o.d.: CrCl 15-50mL/min or body weight <60kg; [7] D: age ≥70 years, CrCl 30-50mL/min, concomitant P-gp inhibitors, or history of GI-bleeding, R: SPC, A: ARISTOTLE, E: SPC; [8] eGFR<30mL/min/1.73m^2; [9] serum creatinine level ≥1.5mg/dl; [10] only patients with CrCl ≥50ml/min; [11] eGFR <60 instead of eGFR <50; [12] stroke; [13] ischemic stroke; [14] stroke, TIA or thromboembolism; [15] ischemic stroke or TIA; [16] stroke or TIA; [17] thromboembolism (arterial); [18] peripheral artery disease; [19] MI and/or peripheral artery disease and/or aortic plaque; [20] MI or arteriosclerosis obliterans; [21] chronic renal failure; [22] renal disease (ICD-9 and ICD-10 codes): moderate (stage III) or severe (stage IV, V); [23] chronic kidney disease (i.e. presence of ICD-10 codes for chronic kidney disease); [24] CrCl <50mL/min; [25] renal disorder; [26] insufficient kidney function; [27] chronic dialysis, renal transplantation or serum creatinine >200mmol/L; [28] hemodialysis; [29] i.e. aspirin; [30] i.e. aspirin, cilostazol, clopidogrel, ticlopidine.

* In case articles concern the same author, a note is added after the author to indicate what makes the articles distinct. Substudies are indented and greyed out. Studies included in the meta-analysis are underlined and presented against a white background; ǂ median instead of mean; ◦ CrCl instead of eGFR.

Supplement 6: Results of risk of bias assessment

			Selection				Comparability	Outcome			Missing data
Author	Year	Reference	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Handling missing data
Arbel	2019	(114)	*	*	*		**	*	*		
Atarashi	2021	(115)	*	*	*		**	*	*		
Briasoulis	2020	(116)	*		*		**	*	*		
Cho	2020	(117)	*		*		**	*	*		
de Groot	2020	(118)	*	*	*			*	*		
Ikeda	2019	(119)	*	*	*		**	*	*		
Inoue	2019	(120)	*	*	*		*	*	*	*	
Inoue	2020	(121)	*	*	*		*	*	*		
Kobayashi	2020	(122)	*	*	*		**	*	*		*
Lee	2017	(123)	*	*	*		**	*	*		
Lee	2019	(124)		*	*	*	**	*	*		
Lee	2021	(125)	*	*	*		**	*	*		
Murata	2019	(126)	*	*	*		**	*	*	*	
Ohno	2020	(127)	*	*	*		**	*	*		*
Salameh	2020	(128)	*	*	*		**	*	*		
Steinberg	2018	(129)	*	*	*		**	*	*	*	*
Tellor	2017	(130)	*		*			*	*		
Yagi	2019	(131)	*	*	*			*	*		
Yao	2017	(132)	*	*	*		**	*	*		

Supplement 7: Results of defining the most homogeneous and best quality studies for meta-analyses

Author*	Year	Reference	Low risk of bias in the representativeness of the exposed and non-exposed cohort (i.e. both awarded with a star according to the NOS)	Uses appropriate guidelines (i.e. SPC, FDA, ESC, EHRA, landmark NOAC trial(s))	Uses a form of propensity adjustment in the analysis of clinical outcomes associated with OLRD and reports a hazard ratio	Belongs to the most homogeneous and best quality studies
Arbel	2019	(114)	Yes	Yes	No	No
Atarashi	2021	(115)	Yes	Yes	No	No
Briasoulis dabigatran/ rivaroxaban	2020	(116)	Yes	No	Yes	No
Briasoulis dabigatran	2020	(116)	Yes	Yes	Yes	Yes
Briasoulis rivaroxaban	2020	(116)	Yes	No	Yes	No
Cho rivaroxaban/ apixaban	2020	(117)	Yes	Yes	No	No
Cho rivaroxaban	2020	(117)	Yes	Yes	Yes	Yes
Cho apixaban	2020	(117)	Yes	Yes	Yes	Yes
de Groot	2020	(118)	Yes	Yes	No	No
Ikeda	2019	(119)	Yes	Yes	Yes	Yes
Inoue	2019	(120)	Yes	No	No	No
Inoue	2020	(121)	Yes	Yes	No	No
Kobayashi	2020	(122)	Yes	No	Yes	No
Lee	2017	(123)	Yes	No	Yes	No
Lee	2019	(124)	No	Yes	Yes	No
Lee	2021	(125)	Yes	Yes	Yes	Yes
Murata	2019	(126)	Yes	No	Yes	No
Ohno	2020	(127)	Yes	No	No	No
Salameh	2020	(128)	Yes	Yes	Yes	Yes

Steinberg	2018	(129)	Yes	Yes	Yes	Yes
Tellor	2017	(130)	Yes	Yes	No	No
Yagi	2019	(131)	Yes	Yes	No	No
Yao dabigatran	2017	(132)	Yes	No	Yes	No
Yao rivaroxaban	2017	(132)	Yes	Yes	Yes	Yes
Yao apixaban	2017	(132)	Yes	No	Yes	No

EHRA = European Heart Rhythm Association; ESC= European Society of Cardiology; FDA = Food and Drugs Administration; i.e. = id est (= that is); NOS = Newcastle-Ottawa quality assessment Scale for cohort studies; NOAC = non-vitamin K antagonist oral anticoagulant; OLRD = off-label reduced dosing; SPC = Summary of Product Characteristics.

* In case articles concern the same author and year, a note is added after the author to indicate what makes the articles distinct.

Supplement 8: Supplemental references

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