Supporting information

Contents

S1. Search strategy

Database search strategy

MEDLINE

Table 1: MEDLINE search strategy

Search strings
1 Atrial Fibrillation/ 2 ((atrial* or atrium or auricular*) adj3 (fibrillat* or flutter*)).ti,ab,kw,kf,ot. 3 NVAF.ti,ab,kw,kf,ot. 4 1 or 2 or 3
5 (Apixaban* or Apixabanum* or Eliques* or Eliquis* or BMS 562247 or BMS-562247 or BMS562247 or 3Z9Y7UWC1J or 503612-47-3).ti,ab,kf,rn,nm. 6 Dabigatran/ 7 (Dabigatran* or Pradaxa* or BIBR 953 or BIBR-953 or BIBR953 or I0VM4M70GC or 211914-51-1).ti,ab,kf,rn,nm. 8 Rivaroxaban/ 9 (Rivaroxaban* or Xarelto* or BAY 59-7939 or BAY 597939 or BAY59-7939 or BAY597939 or BAY-59-7939 or BAY59-7939 or BAY-59-7939 or JNJ-39039039 or JNJ39039039 or 9NDF7JZ4M3 or 366789-02-8).ti,ab,kf,rn,nm. 10 (Edoxaban* or Endoxaban* or Lixiana* or Roteas* or Savaysa* or DU 176 or DU-176 or DU176 or DU 176b or DU-176b or DU176b or NDU3J18APO or 480449-70-5 or 480449-71-6 or 912273-65-5).ti,ab,kf,rn,nm. 11 (oral* adj2 anticoagulant*).ti,ab,kf,rn,nm. Or *Anticoagulants/ad, ae, pk, pd 12 (direct oral anticoagulant* or direct-acting oral anticoagulant* or (DOAC or DOACs)).ti,ab,kf,rn,nm. 13 (Novel Oral Anticoagulant* or New Oral Anticoagulant* or (NOAC or NOACs)).ti,ab,kf,rn,nm. 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 Inappropriate Prescribing/ 16 (dos* or overdosing or underdosing or level*1 or non-recommended or unconventional or off label or (label adj1 adherence)).ti,ab,ot,kw,kf. 17 *Dose-Response Relationship, Drug/ 18 15 or 16 or 17
19 (2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).ed,dc,dp,ep,vd,yr. 20 4 and 14 and 18 and 19

Embase

Table 2: Embase search strategy

Search strings
1 *atrial fibrillation/ 2 ((atrial* or atrium or auricular*) adj3 (fibrillat* or flutter*)).ti,ab,kw,ot 3 NVAF.ti,ab,kw,ot. 4 1 or 2 or 3
5 apixaban/ 6 (Apixaban* or Apixabanum* or Eliques* or Eliquis* or BMS 562247 or BMS-562247 or BMS562247 or 3Z9Y7UWC1J or 503612-47-3).ti,ab,kw,rn,tn,dq,dy,cn 7 dabigatran/ 8 (Dabigatran* or Pradaxa* or BIBR 953 or BIBR-953 or BIBR953 or I0VM4M70GC or 211914-51-1).ti,ab,kw,rn,tn,dq,dy,cn. 9 rivaroxaban/ 10 (Rivaroxaban* or Xarelto* or BAY 59-7939 or BAY 597939 or BAY59-7939 or BAY597939 or BAY-59-7939 or BAY59-7939 or BAY-59-7939 or JNJ-39039039 or JNJ39039039 or 9NDF7JZ4M3 or 366789-02-8).ti,ab,kw,rn,tn,dq,dy,cn. 11 edoxaban/

12 Edoxaban* or Endoxaban* or Lixiana* or Roteas* or Savaysa* or DU 176 or DU-176 or DU176 or DU 176b or DU-176b or DU176b or NDU3J18APO or 480449-70-5 or 480449-71-6 or 912273-65-5).ti,ab,kw,rn,tn,dq,dy,cn 13 (oral* adj2 anticoagulant*).ti,ab,kw,rn,tn,dq,dy,cn 14 *anticoagulant agent/ 15 (direct oral anticoagulant* or direct-acting oral anticoagulant* or (DOAC or DOACs)).ti,ab,kw,rn,tn,dq,dy,cn 16 (Novel Oral Anticoagulant* or New Oral Anticoagulant* or (NOAC or NOACs)).ti,ab,kw,rn,tn,dq,dy,cn 17 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 *inappropriate prescribing/ 19 (dos* or overdosing or underdosing or level*1 or non-recommended or unconventional or off label or (label adj1 adherence)).ti,ab,ot,kw. 20 *dose response/ 21 18 or 19 or 20
22 (2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr.
23 4 and 17 and 21 and 22
24 (conference abstract or conference review).pt.
25 23 not 24
26 limit 25 to embase

Cochrane library

Table 3: Cochrane library search strategy

Search strings
1 MeSH descriptor: [Atrial Fibrillation] this term only 2 ((atrial* or atrium or auricular*) NEAR/3 (fibrillat* or flutter*)):ti,ab 3 NVAF:ti,ab 4 #1 or #2 or #3
5 (Apixaban* or Apixabanum* or Eliques* or Eliquis* or “BMS 562247” or “BMS-562247” or BMS562247 or 3Z9Y7UWC1J or “503612-47-3”):ti,ab 6 MeSH descriptor: [Dabigatran] this term only 7 (Dabigatran* or Pradaxa* or BIBR 953 or “BIBR-953” or BIBR953 or I0VM4M70GC or “211914-51-1”):ti,ab 8 MeSH descriptor: [Rivaroxaban] this term only 9 (Rivaroxaban* or Xarelto* or “BAY 59-7939” or “BAY 597939” or “BAY59-7939” or BAY597939 or “BAY-59-7939” or “BAY59-7939” or “BAY-59-7939” or “JNJ-39039039” or “JNJ39039039” or 9NDF7JZ4M3 or “366789-02-8”):ti,ab 10 (Edoxaban* or Endoxaban* or Lixiana* or Roteas* or Savaysa* or “DU 176” or “DU-176” or “DU176” or “DU 176b” or “DU-176b” or DU176b or NDU3J18APO or “480449-70-5” or “480449-71-6” or “912273-65-5”):ti,ab 11 (oral* NEAR/2 anticoagulant*):ti,ab 12 (direct oral anticoagulant* or direct-acting oral anticoagulant* or (DOAC or DOACs)):ti,ab 13 (Novel Oral Anticoagulant* or New Oral Anticoagulant* or (NOAC or NOACs)):ti,ab 14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15 MeSH descriptor: [Inappropriate Prescribing] this term only 16 (dos* or overdosing or underdosing or level* or non-recommended or unconventional or off label or (label near/1 adherence)):ti,ab 17 #15 or #16
18 #4 and #14 and #17

NB: reviews were selected manually by date of publication 2008-2020.

International Pharmaceutical Abstracts

Table 4: International pharmaceutical abstracts search strategy

Search strings
1 Atrial Fibrillation/ 2 ((atrial* or atrium or auricular*) adj3 (fibrillat$ or flutter$)).ti,ab. 3 NVAF.ti,ab. 4 1 or 2 or 3
5 Apixaban/

6 (Apixaban* or Apixabanum* or Eliques* or Eliquis* or BMS 562247 or BMS-562247 or BMS562247 or 3Z9Y7UWC1J or 503612-47-3).ti,ab. 7 Dabigatran/ 8 (Dabigatran* or Pradaxa* or BIBR 953 or BIBR-953 or BIBR953 or I0VM4M70GC or 211914-51-1).ti,ab. 9 Rivaroxaban/ 10 (Rivaroxaban* or Xarelto* or BAY 59-7939 or BAY 597939 or BAY59-7939 or BAY597939 or BAY-59-7939 or BAY59-7939 or BAY-59-7939 or JNJ-39039039 or JNJ39039039 or 9NDF7JZ4M3 or 366789-02-8).ti,ab. 11 Edoxaban/ 12 (Edoxaban* or Endoxaban* or Lixiana* or Roteas* or Savaysa* or DU 176 or DU-176 or DU176 or DU 176b or DU-176b or DU176b or NDU3J18APO or 480449-70-5 or 480449-71-6 or 912273-65-5).ti,ab. 13 (oral* adj2 anticoagulant*).ti,ab. 14 (direct oral anticoagulant* or direct-acting oral anticoagulant* or (DOAC or DOACs)).ti,ab. 15 (Novel Oral Anticoagulant* or New Oral Anticoagulant* or (NOAC or NOACs)).ti,ab. 16 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 (dos* or overdosing or underdosing or level*1 or non-recommended or unconventional or off label or (label adj1 adherence)).ti,ab.
18 (2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr.
19 4 and 16 and 17 and 18

PubMed (e-pubs only)

Table 5: PubMed search strategy

Search number	Query	Search Details
4	#1 AND #2	“atrial fibrillation”[Title/Abstract] AND “Anticoagulants”[Title/Abstract] AND “dose”[Title/Abstract] AND (“pubstatusaheadofprint”[All Fields] OR “publisher”[Filter] OR “pubmednotmedline”[Filter])
3	#1 AND #2	“atrial fibrillation”[Title/Abstract] AND “Anticoagulants”[Title/Abstract] AND “dose”[Title/Abstract] AND (“pubstatusaheadofprint”[All Fields] OR “publisher”[Filter] OR “pubmednotmedline”[Filter])
2	“pubstatusaheadofprint”[All Fields] OR “publisher”[Filter] OR “pubmednotmedline”[Filter]	“pubstatusaheadofprint”[All Fields] OR “publisher”[Filter] OR “pubmednotmedline”[Filter]
1	((Atrial Fibrillation[Title/Abstract]) AND (Anticoagulants[Title/Abstract])) AND (dose[Title/Abstract])	“atrial fibrillation”[Title/Abstract] AND “Anticoagulants”[Title/Abstract] AND “dose”[Title/Abstract]

NHS EEDs

Table 6: NHS EEDs search strategy

Search strategy
(Atrial Fibrillation) AND (anticoagulant*) AND ((dos* or overdosing or underdosing or level* or non-recommended or unconventional or off label or (label adherence))) IN NHSEED FROM 2008 TO 2020

NB: Searched in ‘Any Field’

Econlit

Table 7: Econlit search strategy

Search strategy
1 TI (((atrial* or atrium or auricular*) N2 (fibrillat* or flutter*))) OR AB (((atrial* or atrium or auricular*) N2 (fibrillat* or flutter*))) Limiters – Published Date: 20080101-20201231
2 TI NVAF AND AB NVAF

Web searching strategy

Table 8: Web searching strategy

Database	Search strategy
Cost-Effectiveness Analysis (CEA) Registry	Searched via http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx The Methods search was use in basic search. The following search term was used: 1. Non-valvular atrial fibrillation
ScHARR HUD	Searched via https://www.scharrhud.org/ 1. Atrial Fibrillation (any field) 2. (dos* or overdosing or underdosing or level* or non-recommended or unconventional or off label or (label adherence)) 1. AND 2.
EconPapers within Research Papers in Economics (RePEc)	Searched via https://econpapers.repec.org/ 1. Atrial Fibrillation AND anticoagulant* AND dos* 2. Non-valvular atrial fibrillation AND anticoagulant* AND Dos* 3. ((Atrial Fibrillation) AND (rivaroxaban OR Xarelto) AND (dos*)) 4. ((Atrial Fibrillation) AND (dabigatran OR Pradaxa) AND (dos*)) 5. ((Atrial Fibrillation) AND (apixaban OR Eliquis) AND (dos*)) 6. ((Atrial Fibrillation) AND (edoxaban OR Lixiana) AND (dos*))

Conference searching strategy

Embase

Table 9: Embase conference searching strategy

Search strings
1 *atrial fibrillation/ 2 ((atrial* or atrium or auricular*) adj3 (fibrillat* or flutter*)).ti,ab,kw,ot. 3 NVAF.ti,ab,kw,ot. 4 1 or 2 or 3
5 apixaban/ 6 (Apixaban* or Apixabanum* or Eliques* or Eliquis* or BMS 562247 or BMS-562247 or BMS562247 or (3Z9Y7UWC1J or 503612-47-3).ti,ab,kw,rn,tn,dq,dy,cn. 7 dabigatran/ 8 (Dabigatran* or Pradaxa* or BIBR 953 or BIBR-953 or BIBR953 or I0VM4M70GC or 211914-51-1).ti,ab,kw,rn,tn,dq,dy,cn. 9 rivaroxaban/ 10 (Rivaroxaban* or Xarelto* or BAY 59-7939 or BAY 597939 or BAY59-7939 or BAY597939 or BAY-59-7939 or BAY59-7939 or BAY-59-7939 or JNJ-39039039 or JNJ39039039 or 9NDF7JZ4M3 or 366789-02-8).ti,ab,kw,rn,tn,dq,dy,cn. 11 edoxaban/ 12 (Edoxaban* or Endoxaban* or Lixiana* or Roteas* or Savaysa* or DU 176 or DU-176 or DU176 or DU 176b or DU-176b or DU176b or NDU3J18APO or 480449-70-5 or 480449-71-6 or 912273-65-5).ti,ab,kw,rn,tn,dq,dy,cn. 13 (oral* adj2 anticoagulant*).ti,ab,kw,rn,tn,dq,dy,cn. 14 *anticoagulant agent/ 15 (direct oral anticoagulant* or direct-acting oral anticoagulant* or (DOAC or DOACs)).ti,ab,kw,rn,tn,dq,dy,cn. 16 (Novel Oral Anticoagulant* or New Oral Anticoagulant* or (NOAC or NOACs)).ti,ab,kw,rn,tn,dq,dy,cn. 17 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 *inappropriate prescribing/ 19 (dos* or overdosing or underdosing or level*1 or non-recommended or unconventional or off label or (label adj1 adherence)).ti,ab,ot,kw. 20 *dose response/ 21 18 or 19 or 20
22 (conference abstract or conference review).pt. 23 4 and 17 and 21 and 22
24 (2018* or 2019* or 2020*).yr.
25 23 and 24

CPCI-S

Table 10: CPCI-S conference searching strategy

Search strings
1 (((atrial* or atrium or auricular*) NEAR/2 (fibrillat* or flutter*))) 2 (NVAF) 3 #2 OR #1
4 ((Apixaban* or Apixabanum* or Eliques* or Eliquis* or BMS 562247 or BMS-562247 or BMS562247 or 3Z9Y7UWC1J or 503612-47-3)) 5 ((Dabigatran* or Pradaxa* or BIBR 953 or BIBR-953 or BIBR953 or I0VM4M70GC or 211914-51-1)) 6 ((Rivaroxaban* or Xarelto* or BAY 59-7939 or BAY 597939 or BAY59-7939 or BAY597939 or BAY-59-7939 or BAY59-7939 or BAY-59-7939 or JNJ-39039039 or JNJ39039039 or 9NDF7JZ4M3 or 366789-02-8)) 7 ((Edoxaban* or Endoxaban* or Lixiana* or Roteas* or Savaysa* or DU 176 or DU-176 or DU176 or DU 176b or DU-176b or DU176b or NDU3J18APO or 480449-70-5 or 480449-71-6 or 912273-65-5)) 8 ((oral* NEAR/3 anticoagulant*)) 9 ((direct oral anticoagulant* or direct-acting oral anticoagulant* or (DOAC or DOACs)))

10 ((Novel Oral Anticoagulant* or New Oral Anticoagulant* or (NOAC or NOACs)))
11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4
12 (Inappropriate Prescribing)
13 ((dos* or overdosing or underdosing or level*1 or non-recommended or unconventional or off label or (label NEAR/2 adherence)).)
14 #13 OR #12
15 #14 AND #11 AND #3
16 #14 AND #11 AND #3 **Refined by: PUBLICATION YEARS:** (2020 OR 2019 OR 2018)

NB: *Indexes=CPCI-S Timespan=All years*

Further conference searches

Table 11: Further conference search strategy

Conference	Search strategy
European Society of Cardiology (ESC)	Handsearched w/c 18th October 2020 Abstracts and posters were searched via the ESC 365 library: https://esc365.escardio.org/Search-Results?vgnextkeyword= The handsearched focused on the inclusion criteria for the review, namely: patients with NVAF and inappropriate dosing.
American College of Cardiology (ACC)	Handsearched w/c 18th October 2020 Abstracts and posters were handsearched via journal as below and then a keyword search was made using the journal interface and a google advanced search. 2020: https://www.onlinejacc.org/content/75/11_Supplement_1 2019: https://www.onlinejacc.org/content/73/9_Supplement_1 2018: https://www.onlinejacc.org/content/71/11_Supplement General resource: https://www.onlinejacc.org/content/meeting-abstract-supplements The handsearched focused on the inclusion criteria for the review, namely: patients with NVAF and inappropriate dosing.
American Heart Association (AHA)	Handsearched w/c 18th October 2020 via journal as below and then a keyword search was made using the journal interface. 2020: event scheduled for Nov 16th (so outside date of search) 2019: https://www.ahajournals.org/toc/circ/140/Suppl_1 2018: https://www.ahajournals.org/toc/circ/138/Suppl_1 The handsearched focused on the inclusion criteria for the review, namely: patients with NVAF and inappropriate dosing.

S2. Study characteristics

Table 12: Summary of study characteristics

Author_year	Study design	Research question	Country	Duration of follow-up	Sample size	DOAC	Patient population	Outcomes/factors	NOS score (categorisation)
Ablefoni_2019	Cross-sectional	3	Germany	N/A	378	RIVA	Consecutive AF patients identified on Heart Centre Leipzig database	eGFR |age | concomitant antiplatelet therapy | HASBLED score |vascular disease |previous stent/PTCA	6 (M)
Ahlert_2018	Cross-sectional	3	United Kingdom	N/A	168	APIX DABI EDOX RIVA	Patients in cardiology ward with DOAC discharge prescriptions	eGFR	6 (M)
Ahmed_2020	Cross-sectional	3	United States	N/A	8576	APIX DABI RIVA	AF patients treated at Mayo clinic with DOACs	Liver disease	5 (M)
Akagi_2019	Cohort	1	Japan	until December 2014	701	DABI	Patients starting dabigatran in study hospitals	Stroke/TIA/SE | major bleeding	5 (M)
Alali_2019	Cohort	3	Saudi Arabia	N/A	151	DABI	Patients receiving dabigatran in outpatient settings	Age | CrCl | CHA2DS2-VASc score | HAS-BLED score | Previous heart failure | History of prior stroke | DM | Hypertension | Peripheral arterial disease | Upper GI bleed	4 (M)
Alcusky_2020	Cohort	1	United States	Median follow up apixaban: 137 (45, 326) | dabigatran 134 (44, 162) | rivaroxaban 139 (42, 374)	21346	APIX DABI RIVA	Nursing home residents aged >65 years	Stroke/TIA/SE | major bleeding | AMI/ VTE/SE | Mortality	5 (M)
Altay_2017	Cross-sectional	3	Turkey	N/A	2862	APIX DABI RIVA	Patients treated with DOAC at study centres	Age | Sex | Chronic renal failure | CHA2DS2-VASc score | HASBLED score | eGFR	5 (M)
Amarenco_2018	Cohort	1	International	1 year	4464	RIVA	NVAF patients >18 with known CrCl	Stroke/SE/TIA/MI | Mortality | Major bleeding, stroke/non-CNS SE, or all-cause death (grouped outcome) | Major bleeding	6 (M)
Andrade_2018	Cross-sectional	3	Canada	N/A	831	APIX DABI EDOX RIVA	Patients with AF and CKD	Use of modified diet in renal disease method to estimate glomerular filtration rate | Use of CKD-EPI to estimate glomerular filtration rate | Use of modified diet in renal disease method to estimate glomerular filtration rate	5 (M)
AndreuCayuelas_2018	Cross-sectional	3	Spain	1 year	692	APIX DABI RIVA	AF patients commencing NOACs in study hospitals	Age | Sex | Weight | Haemoglobin | CHA2DS2-VASc score | Appropriate kidney function monitoring	8 (H)
AndreuCayuelas_2016	Cohort	3	Spain	6 months	162	APIX DABI RIVA	Patients discharged from study hospital	CrCl	4 (M)

Anouassi_2020	Cross-sectional	1	United Arab Emirates	Median 241 days	608	APIX DABI RIVA	NVAF patients receiving DOAC prescription from hospital pharmacy	Ischaemic stroke | Major bleeding	3 (L)
		3						Age | Weight | eGFR | History of major bleeding | CHA2DS2-VASc score | History of prior stroke	2 (L)
Arbel_2019	Cohort	1	Israel	Mean 23 months	8425	APIX DABI RIVA	NVAF patients initiating DOAC therapy	Mortality | Mortality, stroke and myocardial infarction (grouped outcome) | Ischaemic stroke | MI | Major bleeding	7 (H)
Atallah_2020	Cross-sectional	3	United Arab Emirates	Mean 400 days	232	APIX	Patients receiving apixaban from hospital pharmacy	Age | eGFR	6 (M)
Badreldin_2020	Cohort	3	Saudi Arabia	Not recorded	1271	APIX	NVAF patients	Age | weight | History of minor bleed | CrCl | CHA2DS2-VASc score	5 (M)
Bando_2018	Cross-sectional	1	Japan	N/A	1339	RIVA	NVAF patients	Cerebral infarction	7 (H)
Sabbag_2018	Cohort	1	Israel	Mean 2 years	4523	APIX RIVA	AF patients with eGFR 15-60 ml/min	Stroke/SE/death	4 (M)
Basaran_2016	Cross-sectional	3	Turkey	N/A	2086	APIX DABI RIVA	AF patients aged >18	Age | CHA2DS2-VASc score | HASBLED score | Hypertension | History of prior stroke | CrCl	6 (M)
Belen_2015	Cross-sectional	3	Turkey	N/A	174	DABI RIVA	AF patients admitted to study hospital	Age | CrCl | CHA2DS2-VASc score | HASBLED score | CHF | CAD | Hypertension | Cerebrovascular accident	4 (M)
Bosque Varela_2018	Cross-sectional	3	Spain	N/A	341	DOACs (unclear which)	NVAF patients admitted to stroke unit	Age | filtrate glomerular <50 ml/min/1.73m2 and/or creatinine 1.5 mg/dl	5 (M)
Briasoulis_2018	Cross-sectional	3	United States	N/A	51535	DABI RIVA	Newly diagnosed AF patients enrolled in Humana managed care organizations	Age Sex | History of prior stroke | Previous MI | History of major bleeding | Previous heart failure | Moderate to severe chronic kidney disease	4 (M)
Briasoulis_2019	Cross-sectional	1	United States	N/A	55075	DABI RIVA	Newly diagnosed AF patients enrolled in Humana managed care organizations	Intracranial haemorrhage |Medication termination	1 (L)
		3						Age | Sex | Ethnicity | Weight | History of minor bleeding | Previous heart failure	1 (L)
Briasoulis_2020	Cohort	1	United States	Mean 13.9 months for patients eligible for low dose dabigatran | Mean	27747	DABI RIVA	Medicare beneficiaries aged ≥65 with newly diagnosed NVAF	Ischaemic stroke |Major bleeding | Gastrointestinal hemorrhage |Intracranial hemorrhage	8 (H)

		3		15.1 months for patients eligible for standard dose dabigatran | Mean 10.1 months for patients eligible for low dose rivaroxaban | Mean 12.3 months for patients eligible for standard dose rivaroxaban				Age | Sex | Ethnicity | Weight | Smoking | History of prior stroke | History of major bleeding | DM | Previous MI |Liver disease | Previous heart failure | Hypertension | Ischemic cardiomyopathy | Pulmonary circulatory disease | COPD | Valve disease | no or mild renal disease | Moderate renal disease | Severe renal disease | transfusion from procedure | Revascularization | implantable device	9 (H)
Brook_2019	Cohort	1	Australia	Median 17 months	658	APIX DABI RIVA	Patients on DOACs at study hospital	Major bleeding | Ischaemic stroke	5 (M)
Buchholz_2018	Cross-sectional	3	Germany	N/A	569	APIX	AF patients initiated on apixaban in 2016	Age | Weight | Serum Creatinine | CHA2DS2-VASc score | History of prior stroke | Coronary interventions	5 (M)
Camm_2020	Cohort	1	International	2 years	10426	APIX DABI EDOX RIVA	AF patients aged ≥18	Mortality | Stroke/SE | Major bleeding	8 (H)
		3						Age | Sex | Ethnicity | Weight | Acute coronary syndrome | Vascular Disease | History of prior stroke | DM | Moderate to severe chronic kidney disease	8 (H)
Cardoso_2020	Cross-sectional	3	Portugal	N/A	858	APIX DABI EDOX RIVA	NVAF patients	Chronic renal failure | Previous symptomatic haemorrhage | Sex	6 (M)
Chan_2020	Cross-sectional	1	Taiwan	N/A	11275	APIX DABI EDOX RIVA	New onset AF patients aged > 20	Stroke/SE | Major bleeding	7 (H)
Chao_2019	Cross-sectional	3	Korea and Taiwan	N/A	2959	EDOX	NVAF patients	Age | CrCl | History of major bleed | History of prior stroke	4 (M)
Chao_2018	Cohort	1	Taiwan	N/A	2124	RIVA	AF patients aged ≥ 20 treated with RIVA	Ischaemic stroke | Intracranial haemorrhage| Stroke or intracranial haemorrhage	6 (M)
Chao_2020	Cohort	1	International	1 year	26823	EDOX	N/A	Major bleeding | Stroke/SE |Non-major bleeding	4 (M
		3						Age | CrCl | Comorbid conditions | History of major bleeding | History of prior stroke	5 (M)
Cheng_2019	Cohort	1	Taiwan	2.1 years	2214	RIVA	Chinese AF patients aged ≥ 20 with eGFR ≥ 30ml/min	Ischaemic stroke | Intracranial haemorrhage| Stroke or intracranial haemorrhage	8 (H)
Cho_2019	Cross-sectional	1	Not recorded	N/A	741	NOACs	NVAF patients with a CHA2DS2-VASc score of ≥2	NIHSS score | Modified Rankin Scale	4 (M)
Cho_2020	Cohort	1	Korea	15 months	16568	APIX RIVA	NVAF patients newly prescribed NOACs or warfarin	Stroke/SE |Mortality | Major bleeding	8 (H)

Choi_2020	Cohort	3	Korea	10.5 months	3445	APIX DABI RIVA	NVAF patients aged ≥ 18 years	Chronic kidney disease	6 (M)
Davern_2019	Cross-sectional	1	Ireland	N/A	67	NOAC	AF patients receiving OAC presenting with stroke	Ischaemic stroke	4 (M)
Davis_2020	Cohort	1	United States	until OAC discontinuation or study end date	91	APIX DABI EDOX RIVA	AF patients aged > 19 years received one dose of OAC	Major and non-major bleeding	5 (M)
de Almeida_2020	Cohort	1	Portugal	1 year	327	APIX DABI RIVA	Old and frail AF patients prescribed NOAC	Mortality | Stroke/SE/major bleeding	6 (M)
de Groot_2020	Cohort	1	International	1 year	13092	EDOX	AF patients treated with edoxaban	Stroke/SE | major bleeding	6 (M)
		3						Age | Sex | Weight | CHA2DS2-VASc score | HASBLED score | CrCl	7 (H)
Dennehy_2019	Cross-sectional	3	Ireland	N/A	68	APIX DABI RIVA	AF patients eligible for DOAC prescription	Age | no or mild renal disease	4 (M)
Erdogan_2018	Cross-sectional	3	Turkey	N/A	295	NOACs	AF patients aged between 60-99 years being treated with DOACs	Age | Weight | Frailty | Falling/falling-fear | Vascular disease	4 (M)
Essien_2018	Cohort	3	United States	12-24 months	13404	DOACs	AF patients aged ≥ 21 years	Ethnicity	6 (M)
Franchi_2018	Cross-sectional	3	Italy	N/A	328	APIX DABI EDOX RIVA	AF patients aged ≥ 65 years	Weight | Falling/falling-fear | Vascular disease | Liver disease | Percutaneous transluminal coronary angioplasty/coronary artery bypass graft	5 (M)
Gibson_2018	Cross-sectional	1	United States	N/A	556	APIX	NVAF or atrial flutter with patients aged ≥ 18 years receiving at least one dose of apixaban	Major bleeding | Non-major bleeding	4 (M)
		3						Age | Weight | Serum creatinine	5 (M)
Godino_2020	Cohort	1	Italy	2 years	760	APIX DABI EDOX RIVA	NVAF patients treated with NOAC for 3 months	Stroke/SE/TIA/MI | Ischaemic stroke | Stroke/TIA | Ischemic stroke with haemorrhage |TIA | Myocardial infarction | SE | Major and non-major bleeding | Major bleeding | Major bleeding (fatal bleeding) |Intracranial haemorrhage | Mortality (all-cause mortality; cardiac death; bleeding death | cancer death and other) | Thromboembolic events e/o death	6 (M)
		3						Age | Weight | Sex | CrCl | Hypertension | DM | COPD | Peripheral vascular disease | Prior stroke/TIA/SE | Chronic heart failure | Previous bleed | Prior AMI | bioprosthetic	6 (M)

								heart valve | CHA2DS2-VASc score | HASBLED score	
Goena_2019	Cross-sectional	3	Spain	521 days	373	APIX DABI EDOX RIVA	NVAF patients treated with NOAC for stroke prevention	Frailty | History of major bleeding	3 (L)
Gomez Lumbreras_2018	Cohort	3	Spain	1 year	6135	APIX	NVAF patients prescribed apixaban during study period	Treatment naïve	7 (H)
Gronich_2020	Cohort	1	Israel	Through 2018	27765	APIX	Apixaban users with AF diagnosis starting apixaban during the study period	Major bleeding | Ischaemic stroke	7 (H)
Gustafson_2019	Cohort	1	United States	90 days	249	APIX DABI RIVA	Adult NVAF patients discharged with DOAC prescription	Bleeding/thromboembolism/mortality (grouped outcome) | Major and non-major bleeding | Thromboembolism | Mortality	5 (M)
		3						Age | Ethnicity | Sex | Weight | CrCl | Serum creatinine | CHA2DS2-VASc score | Child-Pugh class	6 (M)
Hirsh Raccah_2019	Cross-sectional	3	Israel	N/A	143	APIX DABI RIVA	AF patients aged ≥ 21 years	Age | Sex | Weight | CrCl | Smoking | Serum Creatinine | Hypertension | Hyperlipidemia | CHF | Ischemic heart disease | DM | Chronic renal failure | Cerebrovascular accident	4 (M)
Ikeda_2019	Cohort	1	Japan	1 year	6521	RIVA	NVAF patients with CrCl ≥ 50ml/min starting rivaroxaban	Major and non-major bleeding (any bleeding) | Major bleeding ((Major bleeding was defined as the International Society of Thrombosis and Haemostasis (ISTH) criteria) | Major bleeding (fatal bleeding) | Major bleeding (critical organ bleeding) | Major bleeding (intracranial bleeding) | Major bleeding (Haemoglobin decrease ≥2 g/dL) | Major bleeding (Transfusion of ≥ 2 units of packed RBC or whole blood) | Stroke/SE/MI (Stroke/non-CNS SE/MI) | Ischaemic stroke| Haemorrhagic stroke | SE (non-CNS SE) | Myocardial Infarction | Stroke/SE/MI (Ischemic stroke/non-CNS SE/MI)	5 (M)
		3						Age | Sex | Weight | Serum creatinine | CrCl | CHA2DS2-VASc score | CHADS2 | HASBLED score | CHF | Hypertension | DM | Stroke/TIA | Vascular disease	6 (M)
Inohara_2019	Cohort	1	United States	2 years	6682	APIX DABI EDOX RIVA	AF patients aged ≥ 21 years	Myocardial infarction | Stroke/TIA | Heart Failure | Major bleeding | Mortality (CV death) | Major adverse cardiovascular and neurological event	6 (M)

Inoue_2019	Cohort	1	Japan	460 days	6443	DABI	NVAF patients newly initiated dabigatran treatment for prevention of ischemic stroke and SE	Major bleeding | Intracranial haemorrhage | Gastrointestinal haemorrhage | stroke/TIA/SE | Ischaemic stroke | Haemorrhagic stroke | TIA | SE | Mortality | stroke/TIA/SE/major bleeding/death	5 (M)
		3						Age | Sex | Weight | CHF | DM | Hypertension | History prior stroke | Hepatic disorder | Upper GI bleeding | GI disorder | Serum creatinine | CrCl | CHA2DS2-VASc score | CHADS2 | HASBLED score	5 (M)
Inoue_2020	Cohort	1	Japan	104 weeks	6306	APIX	NVAF patients newly initiated apixaban for prevention of thromboembolism	Major and non-major bleeding (any haemorrhage) | Major bleeding | Intracranial haemorrhage | Intracranial haemorrhage (cerebral haemorrhage; subarachnoid haemorrhage and chronic subdural haemorrhage) | Bleeding (other haemorrhage) | Gastrointestinal haemorrhage | Stroke/TIA/SE | Ischaemic stroke | Ischaemic stroke (atherothrombotic stroke; cardioembolic stroke; Lacunar stroke and other) | SE | TIA	7 (H)
		3						Age | Sex | Weight | Creatinine | CrCl | CHA2DS2-VASc Score | CHADS2 | HASBLED score | Haemorrhage (clinically relevant haemorrhage and haemorrhagic disease) | GI ulcer | History of prior stroke | Hypertension | CHF | DM | Renal disease | Liver disease	7 (H)
Jacobs_2019	Cohort	3	The Netherlands	N/A	3231	APIX DABI RIVA	AF patients prescribed NOAC	Age | Sex |Weight | HASBLED score | Renal function	6 (M)
Jeong_2020	Cohort	1	Korea	1 year	2208	RIVA	NVAF patients	Stroke/SE | Stroke/SE/major bleeding/death (grouped) | stroke/systemic embolism/major bleeding	5 (M)
Jones_2020	Cohort	1	United States	N/A	340	APIX	NVAF patients aged ≥ 18 years receiving apixaban	Major bleeding | Non-major bleeding	4 (M)
Jung_2018	Cross-sectional	1	Korea	N/A	858 (70 on NOACs)	APIX DABI EDOX RIVA	Consecutive NVAF patients suffering acute ischaemic stroke or TIA within 7 days and admitted to study hospitals	Favourable outcome (mRS) (Ischaemic stroke)	4 (M)
		3						Age | Sex | Smoking | CHF | Hypertension | DM | Hyperlipidemia | Ischemic heart disease | Peripheral arterial disease | History of prior stroke | CHA2DS2-VASc score | CE on the TOAST classification | INR | CrCl	4 (M)

Kartas_2019	Cross-sectional	3	Greece	N/A	768	APIX DABI RIVA	NVAF or atrial flutter patients aged ≥ 18 years	Age | History of prior stroke | History of major bleeding | Previous heart failure | CHA2DS2-VASc score | HASBLED score | CrCl	4 (M)
Kato_2018	Cross-sectional	1	Japan	N/A	53	APIX DABI EDOX RIVA	NVAF patients treated with DOACs before onset of stroke	Ischaemic stroke	4 (M)
		3						Age | Sex | Weight | Pre-modified Rankin Scale | Left atrial dimension | Left ventricular ejection fraction Smoking | Hypertension | DM | Dyslipidaemia | History of prior stroke | CAD | CHF | CHA2DS2-VASc score | HASBLED score | creatinine | CrCl	4 (M)
Kawabata_2019	Cohort	1	Japan	8.9 months	1521	APIX DABI EDOX RIVA	NVAF patients with DOAC prescription	Excessive prolongation of coagulation time	4 (M)
Kim_2019	Cohort	1	Korea	7.8 months	687 (403 receiving NOACs)	APIX DABI RIVA	NVAF patients aged ≥ 80 years receiving warfarin or NOACs	Stroke/SE | Major bleeding | Mortality	6 (M)
Kim_2018	Cohort	1	Korea	425 days	1068	APIX DABI RIVA	AF patients administered NOAC during study period	Stroke/SE | Major and non-major bleeding	5 (M)
Larock_2014	Cross-sectional	1	Belgium	N/A	69	DABI RIVA	Patients taking dabigatran or rivaroxaban	Stroke/TIA | DVT/PE | Recuurent atrial thrombus | Non-major bleeding (epistaxis) | Bleeding (melena, hematemesis) | Bleeding (Anaemia) | Bleeding (gynaecological bleeding) | bleeding (gingival bleeding) | Bleeding (hemoptysis) | Major bleeding (haemorrhagic shock) | Major bleeding (death) | Bleeding (Other) | Dyspepsia | Vomiting | Diarrhoea	4 (M)
Leblanc_2020	Cross-sectional	3	Canada	N/A	1681	APIX DABI EDOX RIVA	NVAF or atrial flutter patients aged ≥18 years	Creatinine | Previous bleed | Falling/falling-fear | bleeding risk | Comorbid conditions	5 (M)
Lee_2018	Cross-sectional	3	Korea	N/A	6274	APIX DABI EDOX RIVA	N/A	Sex	4 (M)
Lee_2017	Cohort	1	Korea	1 year	1834 (844 dabigatran)	DABI	AF patients on warfarin or dabigatran with CHA2DS2-VASc score ≥ 2	Thromboembolism | Ischaemic stroke (new-onset stroke) | Ischaemic stroke (embolic stroke) | Major bleeding | Gastrointestinal haemorrhage | Bleeding (Mucosal bleeding) | Mortality (all-cause death) | Major and non-major death (any bleeding) | Non-major bleeding (minor bleeding) | Stroke/SE/major bleeding/death (grouped outcome)| Stroke/systemic embolism/major bleeding (grouped outcome)	7 (H)

Lee_2018	Cohort	1	Not recorded	1 year	2208	RIVA	NVAF patients	Major bleeding	5 (M)
Lee_2019	Cohort	1	Korea	118 months	4325	DOACs	NVAF patients on anticoagulants	Thromboembolism | Major bleeding	4 (M)
Lee_2019	Cohort	1	Korea	N/A	6268	APIX DABI EDOX RIVA	AF patients prescribed DOACs	Thromboembolism | Major bleeding	7 (H)
Lee_2020	Cohort	1	Korea	6.3 months	3733	APIX DABI EDOX RIVA	AF patients on anticoagulants	Thromboembolism | Major bleeding	6 (M)
		3						Age | Sex | Height | Weight | DM | Hypertension | CHF | Prior thromboembolism | Serum creatinine	7 (H)
Lee_2019	Cohort	1	Korea	1.4 years	5196	RIVA	AF patients with CrCl ≥ 50ml/min naïve to rivaroxaban and warfarin	Ischemic stroke | Intracranial haemorrhage | Gastrointestinal haemorrhage | Major bleeding | Mortality (all-cause) | Stroke/ major bleeding/ death (grouped outcome)	6 (M)
Lee_2019	Cohort	1	Korea	N/A	14013	APIX DABI EDOX RIVA	AF patients with body weight ≤ 60kg treated with oral anticoagulants	Ischemic stroke | Intracranial haemorrhage | Gastrointestinal haemorrhage | Major bleeding | Mortality| Stroke/ ICH/bleeding/ hospitalisation/death (grouped outcome)	6 (M)
Lee_2019	Cross-sectional	3	Korea	N/A	3080	APIX DABI EDOX RIVA	Patients prescribed NOAC for stroke prevention	Age | CrCl | Weight | Sex | History of minor bleeding | Hypertension | Stroke/TIA	6 (M)
Leef_2020	Cross-sectional	3	United States	N/A	5060	DABI RIVA	Newly diagnosed NVAF patients seen in an outpatient setting within 90 days following AF diagnosis and prescribed a DOAC within this period	Age | Sex | Ethnicity | CHA2DS2-VASc score | CHADS2 | Charlson comorbidity index | CHF | DM | Hypertension | Stroke/TIA | Previous MI | eGFR	4 (M)
McAlister_2018	Cohort	3	Canada	N/A	6658	APIX DABI RIVA	NVAF patients with a first DOAC diagnosis 2010-2015	Age | Sex | CPCSSN comorbidity | Non-CPCSSN comorbidity | Hypertension | dm | dementia | Peripheral arterial disease | Cerebrovascular accident Previous heart failure	9 (H)
Miyazaki_2020	Cohort	3	Japan	N/A	316	APIX DABI EDOX RIVA	AF diagnosed patients treated with DOACs	HASBLED score	7 (H)
Montrasio_2019	Cohort	1	Switzerland	2.96 years	3267	apixaban | unclear which other DOACs	AF patients on oral anticoagulants	MI/cardiac death/ischemic stroke/systemic embolism (grouped outcome) | Major and non-major bleeding	7 (H)
		3						Coronary heart failure | Coronary artery disease | CKD | Age | Sex | Weight | CHA2DS2-VASc score	7 (H)

Moudallel_2018	Cohort	1	Belgium	N/A	777	APIX DABI RIVA	Patients aged ≥ 60 years admitted to study hospital in 2016 with at least one intake of dabigatran, rivaroxaban or apixaban	Major and non-major bleeding | Thromboembolic events	5 (M)
		3						Physician speciality | Apixaban	6 (M)
Murata_2019	Cohort	1	Japan	39.3 months	1658	APIX DABI EDOX RIVA	NVAF diagnosed patients using any anticoagulant for stroke prophylaxis	Stroke/SE | Major bleeding |Mortality | stroke/SE/major bleeding/death (grouped outcome)	9 (H)
		3						Age | Sex | Height | Weight | High alcohol use | Hypertension | DM | Previous heart failure | Stroke/TIA | Vascular disease | History of major bleeding | CHA2DS2-VASc score | CHADS2 | HASBLED score | CrCl	7 (H)
Navarro_2019	Cohort	1	Spain	20.2 months	2494	APIX DABI EDOX RIVA	NVAF patients receiving DOAC for stroke prevention and SE	Mortality | Ischaemic stroke | Major bleeding | Intracranial haemorrhage	6 (M)
Okumura_2017	Cross-sectional	3	Japan	N/A	3266	APIX DABI EDOX RIVA	AF patients aged ≥ 20 years enrolled in the registry receiving warfarin or DOAC for stroke prophylaxis	Age | Sex | Weight | Current alcohol use | CHADS2 | CrCl	5 (M)
Ortiz_2018	Cross-sectional	3	Spain	N/A	530	APIX DABI RIVA	Adult Spanish AF patients on anticoagulant	Age | Weight CHADS2 | CHA2DS2-VASc score | Charlson comorbidity index | hypertrophic cardiomyopathy | Valve disease |	6 (M)
Pharithi_2019	Cross-sectional	3	Ireland	N/A	348	APIX DABI RIVA	AF patients consecutively prescribed NOACs for primary prevention of stroke with or without planned cardioversion	Anaemia/reduced haemoglobin | Renal function | Previous bleed	4 (M)
Rangnekar_2019	Cross-sectional	3	Australia	N/A	115	DOAC	Patients presenting to the emergency department with a primary diagnosis of AF	Age | Sex | Hypertension | CHF | DM	5 (M)
Salameh_2020	Cohort	1	Israel	5 years	27765	APIX	All CHS adult members aged ≥ 40 years with pre-existing diagnoses of NVAF who are new users of apixaban	Major bleeding | Gastrointestinal haemorrhage | Intracranial haemorrhage | Stroke/SE	8 (H)
Sanghai_2020	Cross-sectional	3	United States	N/A	1064	APIX DABI EDOX RIVA	Ambulatory AF patients aged ≥ 65 years with CHA2DS2VASc score of at least 2	Age | Frailty | Renal function | CHA2DS2-VASc score | Cognitive impairment | Social isolation | Visual impairment | Hearing impairment | Elevated depressive symptoms	5 (M)
Sato_2018	Cross-sectional	1	Japan	N/A	2272	APIX DABI EDOX RIVA	Patients prescribed DOAC for AF	Mortality | Major bleeding | Intracranial haemorrhage | Gastrointestinal	3 (L)

								haemorrhage | Stroke/SE | Ischemic stroke | Haemorrhagic stroke	
		3						Age | Sex | Weight | Creatinine | CHADS2 | HASBLED score	3 (L)
Shamiss_2019	Cross-sectional	3	Not recorded	N/A	629	APIX DABI RIVA	Patients at an AF clinic prescribed low dose DOAC	Age	3 (L)
Shinohara_2019	Cohort	1	Japan	33.1 months	354	APIX DABI EDOX RIVA	AF patients aged > 80 years with non-severe frailty treated with OACs	Major bleeding | Non-major bleeding | Ischemic stroke | SE	6 (M)
		3						Age | Sex | Weight | Frailty | CrCl | CHADS2 | HASBLED score	6 (M)
Shrestha_2018	Cohort	1	United States	12 months	388	APIXDABI EDOX RIVA	Adult NVAF patients aged ≥ 18 years with ≥ 1 pharmacy claim for apixaban, rivaroxaban, or dabigatran	Major bleeding | Ischemic stroke	6 (M)
		3						Age | Sex | Weight | Smoking | Charlson comorbidity index | CHA2DS2-VASc score | CHADS2 | GI bleeding | Intracranial haemorrhage | History of prior stroke | Renal disease | Renal function	7 (H)
Steinberg_2016	Cohort	1	United States	0.99 years	5738	APIX DABI RIVA	Patients treated with NOAC for stroke prevention	Mortality | Stroke/TIA/SE | Myocardial infarction | Hospitalisation (first all-cause hospitalisation; first CV hospitalisation; first bleeding hospitalisation and First nonbleeding, non-CV hospitalization) | First major bleeding | Major bleeding (First bleeding hospitalization or major bleeding)	6 (M)
		3						Age | Sex | Ethnicity | Weight | CrCl | CHA2DS2-VASc score | ORBIT bleeding score | Left ventricular ejection fraction | CAD | Cerebrovascular accident | CHF | GI bleeding	7 (H)
Steinberg_2018	Cohort	1	United States	1 years	7925	APIX DABI EDOX RIVA	Patients treated with NOACs who had follow-up data available	Stroke/TIA/SE | Myocardial infarction | Mortality | Stroke SE/TIA/MI/Death grouped outcomes) | Major bleeding Hospitalisation (bleeding)	6 (M)
		3						Age | Sex | Ethnicity | Frailty | Stroke/TIA | GI bleeding | CHA2DS2-VASc score | ORBIT bleeding score | Left ventricular ejection fraction | CrCl	7 (H)
Stoll_2020	Cohort	1	Germany	3 months	254	APIX DABI RIVA	AF patients admitted with acute cerebral ischemia while taking oral Factor Xa inhibitors	NIHSS score (on admission and at discharge) | Plasma level | Ischemic stroke | Large vessel occlusion | Mortality (in hospital and within 3 months) | Favorable outcomes (mRS) (mRS after 3 months 0-1 and 0-2 or idem	5 (M)
		3						Age | Sex | Weight | Hypertension | DM | Hypercholesterolaemia | History of prior stroke | Thrombectomy | Thrombolysis |	6 (M)

								Renal function | CHA2DS2-VASc score | Pre-modified Rankin scale	
Suwa_2019	Cohort	3	Japan	17	255	APIX RIVA	Outpatients with NVAF undergoing treatment with rivaroxaban or apixaban	Age | Weight | CrCl | CHADS2 | Hypertension | trough plasma concentration	6 (M)
Suzuki_2018	Cohort	1	Japan	N/A	43	APIX DABI EDOX RIVA	NVAF patients treated with a DOAC before the onset of ICH and then admitted to study hospital for ICH	Stroke (GCS score on admission; NIHSS Score and mRD score 0-2 at discharge) | Mortality	5 (M)
		3						Age | Sex | Weight |Smoking | Alcohol intake | Modified Rankin score | Hypertension | DM | Dyslipidemia | Ischemic stroke | Haemorrhagic stroke | CAD | CHF | CHADS2 | CHA2DS2-VASc score | HASBLED score | prothrombin time-international normalized ratio | activated partial thromboplastin time | Serum creatinine | CrCl	6 (M)
Tavares_2020	Cohort	1	Portugal	90 days	156 patients (73 treated with DOAC)	APIX DABI RIVA	Patients who (1) had AIS according to the WHO criteria, (2) were on OAC and the rationale for anticoagulation was NVAF, and (3) information of NIHSS was available on admission	Ischemic stroke | Mortality	5 (M)
Tellor_2017	Cross-sectional	3	United States	495 days	707	APIX	NVAF patients aged ≥ 18 years who received at least 2 doses of apixaban for prevention of stroke and SE	Age | Weight | Dialysis | Serum creatinine | CrCl | CHADS2 | HASBLED score	4 (M)
Umei_2017	Cohort	1	Japan	15.2 (8.4) months dabigatran | 19.6 (7.6) months rivaroxaban | 13.4 (7.5) months apixaban	74	APIX DABI RIVA	NVAF patients who were newly treated with DOACs—dabigatran, rivaroxaban, or apixaban	Thromboembolism | Ischaemic stroke | TIA | SE | Major and non-major bleeding | Major bleeding | Non-major bleeding | Mortality	6 (M)
		3						Age | Sex | Weight | Creatinine | CrCl | CHADS2 | CHA2DS2-VASc score | HASBLED score | Prior stroke/TIA/thromboembolism | Previous bleed	7 (H)
Vinding_2019	Cohort	1	Denmark	N/A	1626	DABI	NVAF patients who switched from VKA to dabigatran after it was approved	Bleeding | Thromboembolic events | Mortality	5 (M)
		3						Age | Sex | High alcohol use | CHF | Hypertension | DM | prior stroke/TIA/thromboembolism | Peripheral arterial disease | Liver disease | CKD | Previous bleed | Cancer | Ischemic heart disease | COPD | CHA2DS2-VASc score | HASBLED score | eGFR	6 (M)

Woo_2019	Cohort	1	Korea	N/A	120	APIX DABI EDOX RIVA	(1) patients with a history of TIA or ischemic stroke, (2) patients taking NOACs for NVAF, and (3) patients diagnosed with cardioembolic stroke	Major vessel occlusion	6 (M)
Yagi_2020	Cohort	1	Japan	683 days	631	RIVA	NVAF patients treated with rivaroxaban	Mortality | Stroke/TIA/SE | Major bleeding |Non-major bleeding	7 (H)
		3						Age | Sex | Weight | CrCl | Hypertension | Anaemia/reduced haemoglobin | CHF	7 (H)
Yao_2017	Cohort	1	United States	3.6 months	14865	APIX DABI RIVA	NVAF patients with creatinine test results who initiated apixaban, dabigatran or rivaroxaban during study period	Stroke/SE | Major bleeding	6 (M)
Yokoyama_2019	Cohort	1	Japan	12 months	85	APIX DABI EDOX RIVA	Acute ischemic stroke patients with nonvalvular atrial fibrillation and at least one cerebral microbleed	Cerebral microbleed	5 (M)
Yu_2019	Cross-sectional	1	Korea	N/A	53649	DOACs	AF patients treated with a NOAC	Stroke/SE | Major bleeding | Mortality	5 (M)
		3						Age | Sex | CHA2DS2-VASc score	5 (M)
Zeymer_2020	Cohort	1	Germany	12 months	1349	APIX	NVAF patients aged > 18 years	Ischemic stroke | Major bleeding | Mortality	6 (M)
		3						Age | Sex | CHA2DS2-VASc score | HASBLED score | History of major bleeding | History of minor bleeding | Severe bleeding under anticoagulation | eGFR	6 (M)

S3. Supplementary figures

Figure 1. Forest plots illustrating odds ratio and 95% CI for factors with a null effect on DOAC underdosing. CI, confidence interval; DOAC, direct oral anticoagulant.

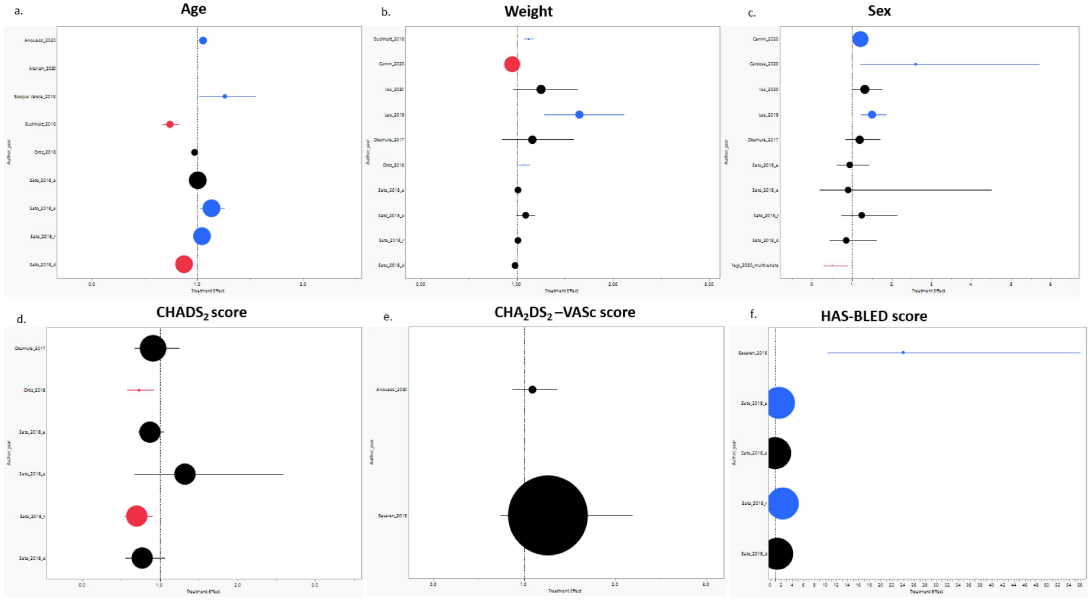


Figure 2. Forest plots illustrating odds ratio and 95% CI for factors with an inconclusive effect on DOAC underdosing. CI, confidence interval; DOAC, direct oral anticoagulant.

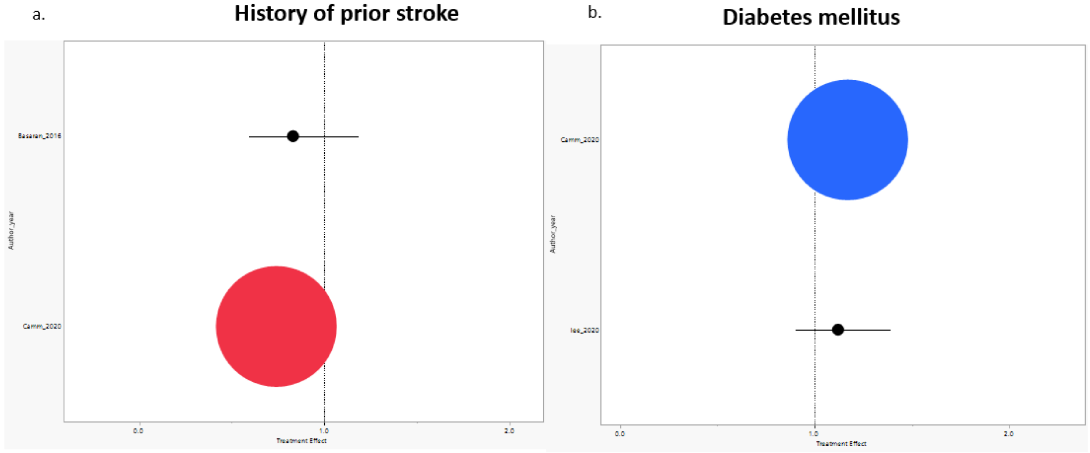


Figure 3: Forest plots illustrating odds ratio and 95% CI for factors with an inconclusive effect on DOAC overdosing. CI, confidence interval; DOAC, direct oral anticoagulant.

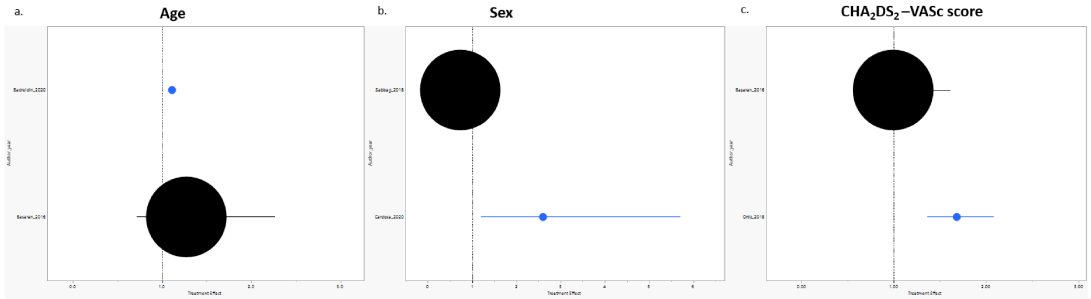
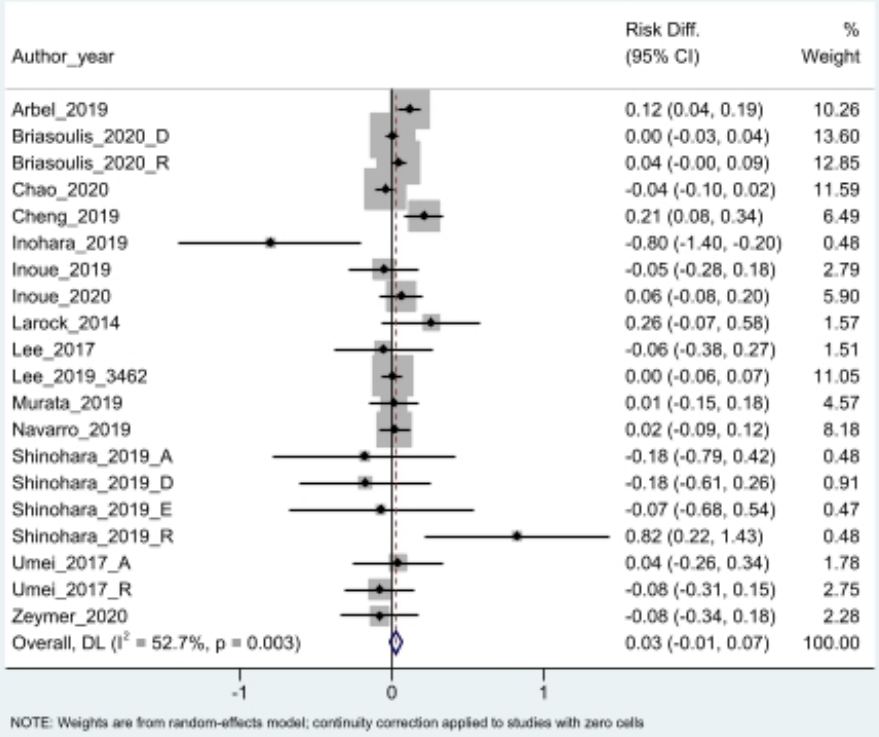


Figure 4. Forest plot displaying absolute risk difference of ischemic stroke and stroke/TIA events among patients given inappropriately low NOAC doses compared to patients given recommended NOAC doses. Data were extracted where available from all included studies and meta-analysis conducted using Stata 16.


Author_year
Risk Diff. (95% CI)
% Weight
Arbel_2019 0.12 (0.04, 0.19) 10.26
Briasoulis_2020_D 0.00 (-0.03, 0.04) 13.60
Briasoulis_2020_R 0.04 (-0.00, 0.09) 12.85
Chao_2020 -0.04 (-0.10, 0.02) 11.59
Cheng_2019 0.21 (0.08, 0.34) 6.49
Inohara_2019 -0.80 (-1.40, -0.20) 0.48
Inoue_2019 -0.05 (-0.28, 0.18) 2.79
Inoue_2020 0.06 (-0.08, 0.20) 5.90
Larock_2014 0.26 (-0.07, 0.58) 1.57
Lee_2017 -0.06 (-0.38, 0.27) 1.51
Lee_2019_3462 0.00 (-0.06, 0.07) 11.05
Murata_2019 0.01 (-0.15, 0.18) 4.57
Navarro_2019 0.02 (-0.09, 0.12) 8.18
Shinohara_2019_A -0.18 (-0.79, 0.42) 0.48
Shinohara_2019_D -0.18 (-0.61, 0.26) 0.91
Shinohara_2019_E -0.07 (-0.68, 0.54) 0.47
Shinohara_2019_R 0.82 (0.22, 1.43) 0.48
Umei_2017_A 0.04 (-0.26, 0.34) 1.78
Umei_2017_R -0.08 (-0.31, 0.15) 2.75
Zeymer_2020 -0.08 (-0.34, 0.18) 2.28
Overall, DL (I^2 = 52.7%, p = 0.003) 0.03 (-0.01, 0.07) 100.00
-1
0
1
NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

S4. Supplementary analysis

Subgroup analysis was conducted for individual DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), and by geographical area (Asian and non-Asian studies).

Stroke outcomes of inappropriate dosing: subgroup analysis

No difference was found in stroke outcomes between different NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) or geographical area (Asian and non-Asian studies).

Bleeding outcomes of inappropriate dosing: subgroup analysis

There was variability with respect to the effect of underdosing on bleeding outcomes when comparing individual NOACs. Subgroup analysis between different NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) found an increased risk of major bleeding with underdosed apixaban (HR=1.35, 95% CI 1.02-1.77; p=0.035). A null effect was found with underdosed dabigatran and rivaroxaban. Subgroup analysis for GIB found a null effect for all underdosed NOACs studied (dabigatran and rivaroxaban). There were insufficient studies to conduct subgroup analysis for ICH based on NOAC.

Overdosing produced the same results for all individually assessed NOACs: a null effect on major bleeding was found for overdosed dabigatran and rivaroxaban.

Mortality outcomes of inappropriate dosing: subgroup analysis

In subgroup analysis, the increased risk of all-cause mortality associated with underdosing was not observed for all individual NOACs. Underdosing with apixaban was associated with an increased risk of all-cause mortality (HR=1.38, 95% CI 1.12-1.70; p=0.436), while a null effect was associated with dabigatran (HR=1.33, 95% CI 0.94-1.88; p=0.103) and rivaroxaban (HR=0.99, 95% CI 0.70-1.40; p=0.965).

The increased risk of all-cause mortality was not observed across all geographical areas. Subgroup analysis by geographical area found an increased risk of all-cause mortality following underdosing for non-Asian studies (HR=1.45, 95% CI 1.30-1.63; p<0.001) but a null effect for Asian studies (HR=1.05, 95% CI 0.76-1.44; p=0.771).

There were insufficient studies to conduct subgroup analysis for mortality as an outcome of overdosing.

Table 13. Hazard ratio (95% CI) identified through subgroup analyses by individual NOAC and geography. N/A indicates that there were insufficient studies available to calculate a hazard ratio (n<2). Outcomes reported as defined in included studies. NOAC, non-vitamin K antagonist oral anticoagulant; IS, ischemic stroke; TIA, transient ischemic attack; SE, systemic embolism.

		Subgroup analysis					
Outcome		**NOAC**				**Geography**	
		Apixaban	**Dabigatran**	**Edoxaban**	**Rivaroxaban**	**Asian**	**Non-Asian**
IS stroke/TIA	Underdosing	N/A	1.12 (0.45-2.82)	N/A	1.22 (0.81-1.83)	0.91 (0.72-1.15)	1.27 (0.83-1.92)
	Overdosing	N/A	1.13 (0.65-1.97)	N/A	0.54 (0.06-4.84)	N/A	N/A
Stroke/SE	Underdosing	1.26 (0.88-1.81)	N/A	N/A	0.80 (0.62-1.02)	0.99 (0.71-1.38)	1.18 (0.65-2.14)
	Overdosing	N/A	N/A	N/A	N/A	N/A	N/A
Major bleeding	Underdosing	1.35 (1.02-1.77)	0.96 (0.74-1.26)	N/A	1.02 (0.87-1.18)	0.96 (0.78-1.17)	1.16 (1.00-1.35)
	Overdosing	N/A	1.32 (0.65-2.67)	N/A	0.9	2.63 (1.06-6.49)	1.36 (0.99-1.86)
Intracranial haemorrhage	Underdosing	N/A	N/A	N/A	N/A	1.13 (0.83-1.55)	1.27 (0.69-2.35)
	Overdosing	N/A	N/A	N/A	N/A	N/A	N/A
Gastrointestinal haemorrhage	Underdosing	N/A	1.06 (0.76-1.50)	N/A	0.91 (0.65-1.29)	0.76 (0.55-1.04)	1.22 (0.96-1.56)

	Overdosing	N/A	N/A	N/A	N/A	N/A	N/A
All-cause mortality	Underdosing	1.38 (1.12-1.70)	1.33 (0.94-1.88)	N/A	0.99 (0.70-1.40)	1.05 (0.76-1.44)	1.45 (1.30-1.63)
	Overdosing	N/A	N/A	N/A	N/A	N/A	N/A

S5. Additional study details

Table 14: Summary of statistical details for studies included in meta-analysis

Reference #	Author, year	Statistical analysis: regression		
		PH test reported	Competing risk analysis reported	Use of time dependent covariate for cumulative NOAC use
10	Steinberg, 2016	NR, but cox PH model used	NR	Not assessed due to availability of dose criteria
12	Yao, 2017	Tested based on Schoenfeld residuals	NR	NR
13	Steinberg, 2018	NR, but cox PH model used	Included cause-specific hospitalization (cardiovascular, bleeding, or non-cardiovascular, non-bleeding), and mortality	NR
14	Lee, 2020	Evaluated using log minus log survival curves	NR	Drug exposure was defined as a time-dependent variable
17	Akcusky, 2020	Evaluated graphically	Used cause-specific hazard ratios to account for competing risks	NR
20	Arbel, 2019	NR	NR	NR
21	Briasoulis, 2020	NR, but cox PH model used	NR	NR
22	Camm, 2020	Tested and also assessed graphically	NR	NR
23	Cho, 2020	NR	NR	NR
24	Ikeda, 2019	NR, but cox PH model used	Cumulative incidence curves used	NR

Reference #	***Author, year***	***Statistical analysis: regression***		
		PH test reported	***Competing risk analysis reported***	***Use of time dependent covariate for cumulative NOAC use***
25	*Kim, 2019*	*NR, but cox PH model used*	*NR*	*NR*
26	*Lee, 2017*	*NR, but cox PH model used*	*Cumulative incidence curves used*	*NR*
27	*Lee, 2019*	*NR, but cox PH model used*	*Cumulative incidence curves used*	*NR*
28	*Murata, 2019*	*NR, but cox PH model used*	*Cumulative incidence curves used*	*NR*
29	*Salameh, 2020*	*NR, but cox PH model used*	*Cumulative incidence curves used*	*NR*

Abbreviations: NR, Not reported; PH, proportional hazards; NOAC, non-vitamin K oral anticoagulant

Table 15: Summary of dosing definition details for studies included in meta-analysis

Reference #	Author, year	NOAC dosing variable		
		Type of dose patients received (initial/maintenance)	How was inappropriate dosing coded?	Dabigatran underdose definition
10	Steinberg, 2016	Maintenance	Initial dosage	110mg (as not approved by FDA)
12	Yao, 2017	Maintenance (New users)	Dose prescribed and based on most recent SCr levels within 1 year of treatment initiation	110mg (as not approved by FDA)
13	Steinberg, 2018	Maintenance	Dose received	75mg
14	Lee, 2020	Maintenance	Dose prescribed	110mg when criteria not met: condition for a reduced dose of dabigatran as an sCCr level ≥30 and <50 mL/min.
17	Akcusky, 2020	Maintenance (New users)	Initial dosage	Unclear
20	Arbel, 2019	Maintenance (New users)	Dosage dispensed immediately prior to outcome event or end of study	110mg reduced dose, "The labeled recommendation for reduced-dose dabigatran is reduced renal function or an increased bleeding risk"
21	Briasoulis, 2020	Maintenance (New users)	Initial dosage based on most recent eGFR prior to treatment initiation	75mg reduced dose "A reduced dose of 75 mg twice daily of dabigatran is recommended to decrease bleeding risk in patients with creatinine clearance (CrCl) 15–30 mL/minute, or co- administration of a strong P-glycoprotein [P-gp] inhibitor (e.g., dronedarone) in patients with CrCl 30–50 mL/minute"
22	Camm, 2020	Maintenance	Dose received	"the European Medicines Agency (EMA) (2), the U.S. Food and Drug Administration (FDA) (3), or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) (4) were reviewed to define recommended dosing, underdosing, or overdosing."
23	Cho, 2020	Maintenance	Dose prescribed	"The authors suggested that the 75 mg dose was suboptimal or patients were treated off-label and under-dosed with the 75 mg dose"
24	Ikeda, 2019	Maintenance (New users)	Prescribed dose	N/A

Reference #	Author, year	NOAC dosing variable		
		Type of dose patients received (initial/maintenance)	How was inappropriate dosing coded?	Dabigatran underdose definition
25	Kim, 2019	Maintenance	Dose received	No under-dosing
26	Lee, 2017	Maintenance	Dose used	"guideline-discordant use of dabigatran 110 mg" 110mg with none of following: old age (>_ 75 years old), renal dysfunction [glomerular filtrationrate (GFR) < 50 mL/min], or low body weight (<50 kg)
27	Lee, 2019	Maintenance	Prescribed dose	110mg
28	Murata, 2019	Maintenance	Dose administered	"Of note, although under-dosing of dabigatran (to 110 mg, b.i.d.) was selected based on the rule previously described (namely, CrCl 30–50 mL/min, age ≥70 years; prior bleeding), rather than based on a standard dose, almost all physicians followed the defined rule for dabigatran under-dosing."
29	Salameh, 2020	Maintenance (New users)	Dose received based on pharmacy records	N/A

Abbreviations: N/A, Not applicable; NOAC, non-vitamin K oral anticoagulant