

**Table 1** Characteristics of included observational studies

Study	Study design	Study period	Region	Data ascertainment	Inclusion criteria	Exclusion criteria	Outcome ascertainment
Abraham 2015[37]	R, C	Nov 2010-Sep 2013	USA	Medical and pharmacy administrative claims from Optum Labs Data Warehouse	≥18y, received dabigatran, rivaroxaban or warfarin on the index date	Patients had Rx for targeted treatment ≤12 months before index date; did not have continuous enrolment; with mechanical heart valve or mitral stenosis, chronic haemodialysis or peritoneal dialysis and kidney transplant; residing in skilled nursing facility or nursing home	ICD-9 codes
Chan 2015[38]	P, C	Oct 2010-Oct 2014	USA	Fresenius Medical Care North America (FMCNA) ESRD database	Chronic haemodialysis patients with AF who started de novo OAC	Patients with a previous diagnosis of warfarin skin necrosis, protein S deficiency, protein C deficiency, or calciphylaxis	Medical records
Chang 2015[39]	R, C	Oct 2010-Mar 2012	USA	IMS Health LifeLink Health Plan Claims Database	≥18y; continuous enrolment in six months before the entry date; receive none NOAC at base line; without bleeding history	Not reported	ICD-9 codes
Graham 2015[26]	R, C	Oct 2010-Dec 2012	USA	Claim files from Medicare beneficiaries enrolled for Medicare program	Patient Aged ≥65y with AF or atrial flutter who newly received ≥1 Rx for dabigatran or warfarin; having ≥6 months of enrolment in Medicare before index date	In a skilled nursing facility or hospice at index, hospitalization that extended beyond the index dispensing date; undergoing dialysis/kidney transplant; with mitral valve disease, heart valve repair or replacement, VTE, or joint replacement surgery in the preceding 6 months	ICD-9 codes
Hernandez 2015[40]	R, C	Oct 2010-Oct 2011	USA	Pharmacy and medical claims of Medicare beneficiaries	Newly diagnosed with AF, filled an outpatient Rx for dabigatran or warfarin within 2 months of the first diagnosis	Filled prescriptions for dabigatran and warfarin during the first 2 months after diagnosis	ICD-9 codes
Larsen 2014[34]	P, C	dabigatran: Aug 2011-May 2013 warfarin: Aug 2009-May 2013	Denmark	Danish National Prescription Registry	Naïve dabigatran users/ any warfarin users during the study period, with a prior diagnosis of AF	With a diagnoses of mitral stenosis, VTE, or valvular surgery; with a previous purchase of phenprocoumon	ICD-10 codes
Staerk 2015[43]	R, C	Aug 2011-Dec 2012	Denmark	The Danish Civil Registration system; Danish National Patient Registry; Danish National Prescription Registry	An OAC naive AF patient initiated first-time OAC or, a warfarin-experienced AF patient initiated dabigatran	Aged <30 or >100; with valvular disease, total hip or knee replacement surgery ≤ 8 weeks or VTE ≤ 6 months before baseline; with GIB, gastroesophageal reflux, gastritis, gastric/duodenal ulcer, gastroscopy, and PPI use 180 days before baseline	ICD-10 codes
Larsen 2013[32]	P, C	Aug 2009-Dec 2012	Denmark	The Danish Civil Registration system; Danish National Patient Registry;	AF patients who were previously untreated (both warfarin and dabigatran)	Not reported	ICD-10 codes

Danish National Prescription Registry

Lauffenburger 2015[41]	R, C	2009-2012	USA	Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement database	AF patients $\geq 18$ y and continuously enrolled for $\geq 12$ months before index date, filling $\geq 1$ Rx for warfarin or dabigatran	Anticoagulant Rx filled in the 12 months prior to the index date, with valvular or transient AF in the baseline period	Validated ICD-9 coding algorithms
Vaughan Sarrazin 2014[36]	R, C	June 2010- June 2011,	USA	National Veterans Affairs administrative encounter and pharmacy data	AF patients who received warfarin for $\geq 180$ days within study period, with the most recent fill date $\leq 90$ d before June 2011	Without a diagnosis of AF during the 12 months before June 2011; with a GFR $< 30$ mL/min/1.73m <sup>2</sup> during the prior 12 months or with a prosthetic heart valve	Validated ICD-9 codes
Laliberte 2014[33]	R, C	May 2011- July 2012.	USA	Symphony Health Solutions' (SHS) Patient Transactional Datasets	AF patients $\geq 18$ y newly initiated on rivaroxaban or warfarin after Nov 2011; CHADS <sub>2</sub> score $\geq 1$ during the 180 days baseline period, $\geq 6$ months of clinical activity	Patients diagnosed at baseline with valvular, pregnancy, malignant cancers and transient causes of AF	ICD-9 codes
Bell 2013[31]	P, CS	Jul 2011- Jun 2012	New Zealand	Medical records from ACH Emergency Department in Auckland, City Hospital	Patients admitted with upper GIB and concurrent warfarin or dabigatran therapy	Not reported	Hospital admission records
Choi 2014[60]	P, CS	Sept 2011- Nov 2011	USA	The National Health and Wellness Survey, Lightspeed Research Internet panel, Telephone databases of AF patients	Patients $\geq 18$ years with self-reported AF diagnosed by healthcare provider, had used warfarin or dabigatran as stroke prophylaxis.	Less technologically able patients	Self-reported
Sherid 2015[42]	R, CS	Oct 2010- Oct 2012	USA	Medical records from CGH Medical Center in Sterling, Ill. & Saint Francis Hospital in Evanston, Ill.	Patients aged $\geq 18$ y taking either dabigatran for $\geq 3$ days or rivaroxaban for $\geq 4$ days	An unknown duration of rivaroxaban and dabigatran, lack of follow-up, with pregnancy, mechanical valve replacement and advanced kidney disease (GFR $< 15$ ml/min/1.73 m <sup>2</sup> ) or end-stage renal disease on dialysis	Medical records
Nagao 2015[45]	R, CS	Apr 2013- Mar 2014	Japan	Medical records from Nagoya University Hospital,	Patients who received warfarin or apixaban, and underwent radiofrequency catheter ablation for AF	Not reported	Medical records
Sherid 2014[35]	R, CS	Oct 2010- Apr 2013	USA	Medical records from CGH Medical Center in Sterling, Ill. & Saint Francis Hospital in Evanston, Ill.	Patients aged $\geq 18$ y taking either dabigatran for $\geq 3$ days or rivaroxaban for $\geq 4$ days	An unknown duration of rivaroxaban and dabigatran, lack of follow-up, pregnancy, mechanical valve replacement and advanced kidney disease (GFR $< 15$ ml/min/1.73 m <sup>2</sup> or end-stage renal disease on dialysis)	Medical records

**Abbreviations:** ACH= Auckland City Hospital; AF=atrial fibrillation; C=cohort; CS=cross-sectional; FDA=Food and Drug Administration; GFR= glomerular filtration rate; GI=gastrointestinal; GIB=gastrointestinal bleeding; ICD-9=International Classification of Diseases, Ninth Revision; P=prospective; R=retrospective; VTE=venous thromboembolism; OAC=oral anticoagulation; Rx=prescription; IMS=Intercontinental Marketing Services; ESRD=end-stage renal disease; Y=years; CHADS<sub>2</sub>=congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism; PPI=proton pump inhibitor

**Table 2 Subgroup and sensitivity analyses of the GIB risk among users of NOAC vs warfarin**

Sensitivity analyses		Comparison groups	No. of studies	Adjusted estimate (95%CI)	Heterogeneity between studies
Sensitivity analysis 1 <sup>a</sup>		dabigatran vs warfarin	7	1.30 (1.01-1.66)	P<0.00001, I <sup>2</sup> =91%
Sensitivity analysis 2 <sup>b</sup>		dabigatran vs warfarin	7	1.24 (0.98-1.59)	P<0.00001, I <sup>2</sup> =91%
Sensitivity analysis 3 <sup>c</sup>		dabigatran vs warfarin	6	1.27 (1.13-1.41)	P=0.09, I <sup>2</sup> =48%
Sensitivity analysis 4 <sup>d</sup>		dabigatran vs warfarin	6	1.18 (1.02-1.36)	P=0.004, I <sup>2</sup> =71%
		rivaroxaban vs warfarin	4	1.10 (0.87-1.38)	P=0.28, I <sup>2</sup> =22%
Subgroup analyses			No. of studies	Adjusted estimate (95%CI)	Heterogeneity between groups
Variable	Subgroups				
<b>Indication</b>	Dabigatran	AF	6	1.21 (1.03-1.42)	P=0.99, I <sup>2</sup> =0%
		Non-AF	1	1.14 (0.54-2.39)	
		Non-specified	1	1.21 (0.96-1.53)	
	Rivaroxaban	AF	3	1.08 (0.87-1.35)	
		Non-AF	1	0.89 (0.60-1.32)	
		Non-specified	1	0.98 (0.36-2.69)	
<b>GIB severity</b>	Dabigatran	Major	2	1.30 (1.17-1.46)	P=0.33, I <sup>2</sup> =10.3%
		Non-major	1	0.85 (0.40-1.79)	
		Any	5	1.15 (0.95-1.40)	
	Rivaroxaban	Major	1	0.96 (0.58-1.59)	
		Non-major	1	0.82 (0.30-2.22)	
		Any	3	1.10 (0.87-1.38)	
<b>Patient age</b>	Dabigatran	18-64y	1	1.34 (0.98-1.83)	P=0.63, I <sup>2</sup> =0%
		≥ 65y	3	1.46 (0.99-2.13)	
		All adults ≥ 18y	6	1.21 (1.00-1.45)	
	Rivaroxaban	18-64y	1	1.03 (0.33-3.18)	
		≥ 65y	2	1.49 (0.33-6.68)	
		All adults ≥ 18y	4	1.09 (0.92-1.30)	
<b>Prior use of warfarin</b>	Dabigatran	Yes	2	1.40 (1.01-1.96)	P=0.31
		No	6	1.16 (1.01-1.34)	I <sup>2</sup> =3.0%
<b>NSAID</b>	Dabigatran	Yes	5	1.20 (0.98-1.47)	P=0.87
		No	2	1.24 (0.94-1.63)	I <sup>2</sup> =0%

	Rivaroxaban	Yes	3	1.10 (0.87-1.38)	P=0.63
		No	1	0.96 (0.58-1.59)	I <sup>2</sup> =0%
<b>PPI/H2</b>	Dabigatran	Yes	4	1.11 (0.95-1.30)	P=0.01
		No	3	1.50 (1.25-1.80)	I <sup>2</sup> =83.8%
	Rivaroxaban	Yes	2	0.93 (0.70-1.24)	P=0.17
		No	2	1.20 (0.96-1.50)	I <sup>2</sup> =46.7%
<b>Antiplatelet agents</b>	Dabigatran	Yes	5	1.17 (0.99-1.40)	P=0.43
		No	2	1.31 (1.07-1.59)	I <sup>2</sup> =0%
	Rivaroxaban	Yes	2	1.10 (0.81-1.49)	P=0.64
		No	2	0.96 (0.61-1.51)	I <sup>2</sup> =0%
<b>Steroid</b>	Dabigatran	Yes	3	1.09 (0.83-1.43)	P=0.26
		No	4	1.33 (1.07-1.64)	I <sup>2</sup> =20.9%
	Rivaroxaban	Yes	2	0.93 (0.70-1.24)	P=0.17
		No	2	1.20 (0.96-1.50)	I <sup>2</sup> =46.7%
<b>SSRI</b>	Dabigatran	Yes	2	1.02 (0.64-1.64)	P=0.37
		No	5	1.28 (1.10-1.50)	I <sup>2</sup> =0%
	Rivaroxaban	Yes	1	0.93 (0.69-1.25)	P=0.19
		No	3	1.19 (0.96-1.48)	I <sup>2</sup> =42.4%

<sup>a</sup> substitution of Larsen 2014's results [34] with that of Staerk 2015[43], and Graham 2015's results [26] with that of Hernandez 2015[40], respectively

<sup>b</sup> substitution of Larsen 2014's results [34] with that of Larsen 2013[32], and Graham 2015's results [26] with that of Hernandez 2015[40], respectively

<sup>c</sup> exclusion of the result of Abraham 2015 [37]

<sup>d</sup> exclusion of the result of Chan 2015 [38]

**Abbreviations:** NOAC= non-vitamin K antagonist oral anticoagulants; GIB=gastrointestinal bleeding; PPI=proton pump inhibitor; H2RA=histamine type-2 antagonists; NSAID=non-steroidal anti-inflammatory drug; Riva=rivaroxaban; Dabi=dabigatran; Warf=warfarin; RR=risk ratio; CI=confidence interval; SSRI=selective serotonin reuptake inhibitor