

ESM 1. Supplementary Table 1a. Study characteristics: Design, methodology, region and data source, enrollment period, and duration of follow up (d...days, m...months, y...years).

Study	Ref	Design	Methodology	Evaluated endpoints	Drugs	Region/data source	Enrollment period	Duration of follow up
Amin 2013	(22)	RR	Crude rates	Stroke, Major bleeding	V	US / Medco database	Jan 2007-Jun 2010	1.8 y
Larsen 2013	(23)	RC	PSM	Stroke, Major bleeding, IC bleeding, Deaths, MI	DV	DK / Nationwide database	Jun 2012-Dec 2013	1.2 y
Sörensen 2013	(24)	RC	CA	Major bleeding	DV	DK / Nationwide database	Aug 2011-Dec 2011	6 m
Southworth 2013	(25)	RC	Crude rates	IC bleeding, GI bleeding	DV	US / Mini-sentinel distributed database	Oct 2010-Dec 2011	100 d
Bengtson Abstract 2014	(26)	RC	PSM	Stroke, IC bleeding, GI bleeding	DRV	US / MarketScan Commercial and Medicare Supplemental databases	2010-2012	1.6 y
Beyer-Westendorf 2014	(27)	PR	Crude rates	Major bleeding, NMCR	R	Germany / Dresden registry of daily care patients	Oct 2011-Dec 2013	12 m
Fontaine 2014	(28)	RC	Crude rates	Major bleeding	DR	US / Intermountain healthcare records	Oct 2010-Nov 2012	2.0 y
Laliberte 2014	(29)	RC	PSM	Stroke/SE, Major bleeding, IC bleeding	RV	US / Symphony health solutions' patient transactional datasets	Nov 2011-Jul 2012	98 d
Larsen 2014	(30)	RC	PSM	Major bleeding, IC bleeding	DV	DK / Nationwide database	Aug 2011-Dec 2012 (D)	1.7 y

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							Aug 2009-Dec 2010 (V)	
Navgren 2014	(31)	PR	Crude rates	Major bleeding, IC bleeding	V	Sweden / Anticoagulation clinic Helsingborg	Nov 2007-Nov 2010	1.9 y
Ogawa 2014	(32)	PR	Crude rates	Stroke, Major bleeding, MI, NMCR	R	Japan / Post marketing surveillance registry	Apr 2012-Dec 2013	6 m
Siu 2014	(33)	RR	Crude rates	IC bleeding	V	Hong Kong / Queen Mary hospital database	Jul 1997-Dec 2011	3.2 y
Tran 2014	(34)	RR	Crude rates	GI bleeding	D	US / Single hospital database	Jan 2011-Dec 2011	10 m
Yap 2014	(35)	PR	Crude rates	Major bleeding	D	Malaysia / National health instute hospital	Oct 2012-Mar 2013	10 m
Abraham 2015	(36)	RC	PSM	Stroke, GI bleeding	DRV	US / Optumlabs data warehouse database	Nov 2010-Sep 2013	1.1 y
Avgil-Tsadok 2015	(37)	RC	PSW	Stroke, Bleeding, Deaths, MI	DV	Canada / Quebec hospital discharge database	Jan 1999-March 2013	7 m
Bouillon 2015	(38)	RMC	CA	Stroke/SE, Major bleeding, MI	DRV	France / Nationwide health-insurance database	Jan 2011-Nov 2012	10 m

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Chang 2015	(39)	RC	PSW	GI bleeding	DRV	US / IMS health lifelink health plan claims database	Oct 2010-Mar 2012	47 d
Engelberger 2015	(40)	PC	Crude rates	Stroke/SE, Major bleeding	R	CH / 115 primary care physicians	Jan 2012-May 2013	96 d
Graham 2015	(41)	RC	PSM	Stroke, IC bleeding, Deaths, Hospitalized bleeding, MI	DV	US / Medicare database	Oct 2010-Dec 2012	62 d
Granziera 2015	(42)	RR	Crude rates	Major bleeding, IC bleeding, GI bleeding	V	Italy / Anticoagulation Centre at Padua University Hospital	Jan 2007-Jan 2012	2.2 y
Hernandez 2015	(43)	RC	PSW	Major bleeding, IC bleeding	DV	US / Medicare database	Oct 2010-Oct 2011	7 m
Ho 2015	(44)	RC	Crude rates	Stroke/SE, IC bleeding, Deaths	DV	Hong Kong / Hospital based registry	Jul 1997-Dec 2012	3.0 y
Jacobs Abstract 2015	(45)	RC	PSM	Stroke/TIA, Major bleeding, Deaths	DV	US	Jun 2010-Dec 2014	6 m
Kamble Abstract 2015	(46)	RC	CA	Major bleeding	DRAV	US / MarketScan commercial & Medicare databases	Jan 2012-Dec 2013	4 m
Lauffenburger 2015	(47)	RC	PSW	Stroke, GI bleeding, MI	DV	US / MarketScan commercial & Medicare databases	Oct 2010-Dec 2012	12 m

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Leef 2015	(48)	RC	PSM	Deaths	DV	US / University of Pittsburgh Medical Center	Jan 2006-Nov 2013	3.5 y
Lin Abstract 2015	(49)	RC	CA	Major bleeding	DRAV	US / Humedica de-identified Electronic Health Record database	Jan 2013-Jun 2014	6 m
Maura 2015	(50)	RC	PSM	Stroke/SE, Bleeding	DRV	France / Nationwide French National Health Insurance information system & French Hospital Discharge database	Jul 2011-Nov 2011 Jul 2012-Nov 2012	83 d
Sjögren 2015	(51)	RR	Crude rates	Stroke/SE/TIA, IC bleeding, Bleeding, MI	V	Sweden / Auricula, Swedish national register for atrial fibrillation & Patient register	Jan 2006-Dec 2011	2.8 y
Tamayo 2015	(52)	PR	Crude rates	Major bleeding, IC bleeding	R	US / Department of Defense EMRs	Jan 2013-March 2014	8 m
Verdecchia 2015	(53)	PR	Crude rates	Stroke, Major bleeding	D	Italy / Umbria AF registry	Jul 2013-?	6 m
Adeboyeje Abstract 2016	(54)	RC	PSW	Stroke/SE, Major bleeding	DRAV	US / U.S. commercial claims database	Nov 2010-Feb 2015	10 m

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Arihiro 2016	(55)	PC	PSW	Stroke/SE, Major bleeding, IC bleeding, Deaths	DV	Japan /18 stroke centers across Japan	Sep 2011-Mar 2014	91 d
Avgil-Tsadok 2016	(56)	PC	PSW	Stroke/TIA, Major bleeding, IC bleeding, GI bleeding	DV	Canada / Quebec health databases	Apr 2011-Mar 2013	2.5 y
Blin 2016	(57)	RR	Crude rates	Major bleeding, Deaths, MI	V	France /Echantillon Généraliste de Bénéficiaires healthcare claims and hospitalization database	Jan 2007-Dec 2011	2.4 y
Camm (XANTUS) 2016	(58)	PC	Crude rates	Stroke, Stroke/SE, Major bleeding, IC bleeding, Deaths, MI, NMCR	R	International / Multicenter	Jun 2012-Dec 2013	11 m
Chan EW 2016	(59)	RR	PSM	Stroke, IC bleeding, GI bleeding, Deaths	V	Hong-Kong / Hospital Authority database	Jan 2010-March 2013	1.8 y
Chan YH 2016a	(60)	RC	PSM	Stroke/SE, Major bleeding, IC bleeding, GI bleeding, Deaths, MI	DRV	Taiwan / National Health Insurance Research Database	Feb 2013-Dec 2013	12 m
Chan YH 2016b	(61)	RC	PSW	Stroke, Major bleeding, IC bleeding, GI bleeding, Deaths, MI	DV	Taiwan / National Health Insurance Research Database	Jun 2012-Dec 2013	8 m
Coleman (REVISIT-US) 2016	(62)	RC	PSM	Stroke, IC bleeding	RAV	US / MarketScan claims databases	Jan 2012-Oct 2014	9 m
Coleman (RELIEF) 2016	(63)	RC	PSM	Stroke/SE/CH/MI, IC bleeding	RV	Germany / Primary Care Physician	Jan 2012-Oct 2013	12 m

Study	Ref	Design	Methodology	Evaluated endpoints	Drugs	Region/data source	Enrollment period	Duration of follow up
						Panel longitudinal database		
Ellis 2016	(64)	RC	Crude rates	Major bleeding, IC bleeding, GI bleeding	DRV	Israel / Israeli Clalit Health Services database	Jan 2012-Jun 2013	8 m
Gorst-Rasmussen 2016	(65)	PC	PSW	Stroke/SE/TIA, IC bleeding, GI bleeding, Deaths, MI	DRV	Denmark / Merged nationwide registries	Feb 2012 -Aug 2014	2.2 y
Graham 2016	(66)	RC	PSW	Stroke, Major bleeding, IC bleeding, GI bleeding, Deaths, MI	DR	US / Medicare database	Nov 2011-Jun 2014	4 m
Hecker 2016	(67)	PR	Crude rates	Stroke/SE/TIA, Major bleeding, IC bleeding, Acute coronary syndrome, NMCR	R	Germany / Dresden NOAC Registry	Oct 2011-Feb 2013	2.2 y
Korenstra 2016	(68)	RC	PSM	Stroke/SE, Major bleeding	DV	Netherlands / Martini Hospital Groningen	Jan 2010-Dec 2012	1.5 y
Kwon 2016	(69)	RC	CA	Stroke/SE, Major bleeding	DV	South Korea / Hospital database	Jan 2011-Sep 2014	12 m
Larsen 2016	(70)	RC	PSW	Stroke/SE, Major bleeding, IC bleeding, Deaths	DRAV	Denmark / Merged nationwide registries	Aug 2011- Oct 2015	10 m
Lip 2016a	(71)	RC	PSM	Major bleeding	DRAV	US / MarketScan and Medicare databases	Jan 2013-Dec 2014	4 m
Lip 2016b	(72)	RC	CA	Major bleeding	DRAV	US / MarketScan and Medicare databases	Jan 2013-Dec 2013	8 m

Study	Ref	Design	Methodology	Evaluated endpoints	Drugs	Region/data source	Enrollment period	Duration of follow up
Nishtala 2016	(73)	RC	PSM	IC bleeding, GI bleeding, Bleeding	DV	NZ / National Minimum Dataset	Jul 2011-Dec 2012	9 m
Noseworthy 2016	(74)	RC	PSM	Stroke/SE, Major bleeding, IC bleeding	DRA	US / OptumLabs Data Warehouse database	Oct 2010-Feb 2015	10 m
Seeger 2016	(75)	SC	PSM	Stroke/SE, Major bleeding, IC bleeding, GI bleeding, MI	DV	US / MarketScan and Clinformatics databases	Oct 2010-Dec 2012	5 m
Tziomalos 2016	(76)	PC	Crude rates	Stroke, Deaths, MI	DV	Greece / Single hospital database	Sep 2010 -Jun 2013	12 m
Villines 2016	(77)	RC	PSM	Stroke, Major bleeding, IC bleeding, Deaths, MI	DV	US / Departement of Defense claims database	Oct 2010-Jul 2012	8 m
Yao 2016	(78)	RC	PSM	Stroke/SE, Major bleeding, IC bleeding	DRAV	US / OptumLabs Data Warehouse database	Oct 2010-Jun 2015	11 m
Yap 2016	(79)	RC	CA	Stroke, Major bleeding, GI bleeding	DV	Malaysia / Malaysia's National Heart Institute	Jan 2009-Dec 2013	11 m
Yavuz 2016	(80)	PC	UA	Stroke, Major bleeding, IC bleeding, GI bleeding, Deaths, MI	DV	Turkey / Four hospitals	May 2013-Nov 2014	11 m
Yoshimura 2016	(81)	PC	PSW	Stroke/TIA, Major bleeding, IC bleeding, Deaths	DV	Japan / SAMURAI-NVAF registry	Sep 2011-Mar 2014	12 m
Abraham 2017	(82)	RC	PSM	GI bleeding	DRA	US / OptumLabs Data Warehouse database	Oct 2010-Feb 2015	8 m

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Adeboyeje 2017	(83)	RC	PSW	IC bleeding, GI bleeding	DRAV	US / HealthCore Integrated Research Environment database	Nov 2010-Feb 2015	2.3 y
Amin 2017	(84)	RC	PSM	Stroke/SE, Major bleeding	DRAV	US / Medicare database	Jan 2013-Dec 2014	6 m
Bengtson 2017	(85)	RC	PSW	Stroke, IC bleeding, GI bleeding, MI	DV	US / MarketScan databases	Jan 2009-Dec 2012	1.7 y
Cha 2017	(86)	RC	PSM	Stroke, IC bleeding, Deaths	DRAV	Korea / National Health Insurance Service database	Jan 2014-Dec 2015	9 m
Coleman (REASSESS) 2017	(87)	RC	PSM	Stroke, Major bleeding, IC bleeding, MI	AV	Germany / Primary Care Physician panel	Jan 2013-Aug 2014	11 m
Coleman 2017	(88)	RC	PSM	Stroke, IC bleeding, MI	AV	Germany / Primary Care Physician panel	Jan 2013-Mar 2015	12 m
Coleman (REAFFIRM) 2017	(89)	RC	PSM	Stroke, Major bleeding, IC bleeding	DRAV	US / MarketScan databases	Jan 2012-Jun 2015	10 m
Deitelzweig 2017	(90)	RC	PSM	Stroke/SE, Major bleeding, IC bleeding, GI bleeding	AV	US / Medicare database	Jan 2013-Sep 2015	7 m
Denas 2017	(91)	RC	PSM	Stroke, IC bleeding, Deaths, MI	DV	Italy / Veneto region databases	Jul 2013-Dec 2015	1.3 y
Halvorsen 2017	(92)	PC	CA	Major bleeding, IC bleeding, GI bleeding, NMCR	DRAV	Norway / Norwegian Patient Registry and Norwegian	Jan 2013-Jun 2015	6 m

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						Prescription Database		
Hohnloser 2017	(93)	RC	CA	Major bleeding, GI bleeding	DRAV	Germany / database from the Health Risk Institute	Jan 2013-Mar 2015	1.1 y
Kohsaka 2017	(94)	RC	PSM	Major bleeding	DRAV	Japan / health claim and diagnostic procedure combination database	Mar 2011-Mar 2016	1.5 y
Lamberts 2017	(95)	RC	CA	Major bleeding	DRAV	Denmark / Merged nationwide registries	Aug 2011-Dec 2015	1.0 y
Leschke (XANTUS-DE) 2017	(96)	PC	Crude rates	Stroke/SE, Major bleeding, IC bleeding, Deaths, MI	R	Germany / XANTUS investigators	Jun 2012-Feb 2015	12 m
Li W-H 2017	(97)	PR	Crude rates	Stroke, IC bleeding	DRV	Hong Kong / Hospital based registry	Jan 2008-Dec 2014	1.8 y
Li X 2017	(98)	RC	PSM	Stroke/SE, Major bleeding, IC bleeding, GI bleeding	AV	US / MarketScan, PharMetrics, Optum, and Humana databases	Jan 2013-Sep 2015	5 m
Lin 2017	(99)	RC	PSM	Major bleeding	DRAV	US / IMS Pharmetrics Plus database	Jan 2013-Sep 2015	1.0 y

Study	Ref	Design	Methodology	Evaluated endpoints	Drugs	Region/data source	Enrollment period	Duration of follow up
Naganuma 2017	(100)	RC	PSM	Stroke/SE/TIA, Major bleeding	DV	Japan / single hospital database	Mar 2011-Dec 2013	10 m
Nielsen 2017	(101)	RC	PSW	Stroke/SE, Major bleeding, Deaths	DRAV	Denmark / Merged nationwide registries	Aug 2011-Feb 2016	1.5 y
Norby 2017	(102)	RC	PSM	Stroke, IC bleeding, GI bleeding, MI	DRV	US / MarketScan database	Jan 2010-Dec 2014	2.2 y
Noseworthy 2017	(103)	RC	Crude rates	Stroke/SE, Major bleeding	DRAV	US / OptumLabs Data Warehouse database	Jul 2006-Jun 2016	3.0 y
Peacock 2017	(104)	RR	Crude rates	Major bleeding, IC bleeding, GI bleeding	R	US / US Department of Defense health care database	Jan 2013-Jun 2015	1.1 y
Russo-Alvarez 2017	(105)	RC	PSM	Stroke/SE/TIA, Major bleeding	RV	US / Cleveland Clinic Health System database	Jan 2012 -Jul 2016	1.2 y
Staerk 2017	(106)	RC	CA	Stroke, Stroke/SE, IC bleeding	DRAV	Denmark / Merged nationwide registries	Mar 2012-Dec 2016	11 m
Weir 2017	(107)	RC	PSW	Stroke, Major bleeding	RV	US / Optum's Integrated Claims-Clinical de-identified dataset	May 2011-Aug 2014	7 m
Yamashita 2017	(108)	PC	PSM	Stroke/SE, Major bleeding	DV	Japan / Fushimi AF Registry	?-Nov 2015	2.7 y

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Yiginer 2017	(109)	PC	CA	Major bleeding, IC bleeding, GI bleeding, Deaths	DR	Turkey / 5 tertiary hospitals	NS	1.4 y

Design: RC...retrospective cohort; PC...prospective cohort; RMC...retrospective matched cohort; SC...sequential cohort; RR...retrospective registry; PR...prospective registry study. Methodology: PSM...propensity score matching; PSW...propensity score weighting/adjustment; CA...confounder adjustment. Evaluated endpoints: SE...systemic embolism; IC...intracranial; GI...gastrointestinal; MI...myocardial infarction. AF...Atrial fibrillation; EMR...Electronic medical records