Controversies in Anticoagulation : Optimizing Outcome in NOACs for GI Bleeding Risk

Boyoung Joung, MD, PhD

Professor, Division of Cardiology
Director of Electrophysiology Laboratory
Severance Cardiovascular Hospital
Yonsei University College of Medicine

All Licensed Anticoagulants Deliver Greater Benefit than Risk, NOACs More than VKAs : Achilles hill of NOAC

NOACs are associated with significant reductions in:

- Haemorrhagic stroke (with a strong trend towards lower rates of ischaemic stroke)
- Intracranial haemorrhage
- All-cause mortality (with a trend towards lower rates of myocardial infarction)

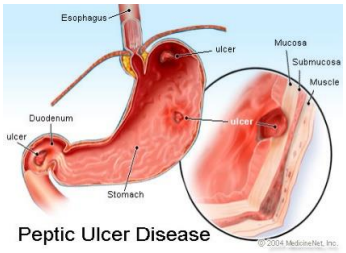
Whereas the **risk of gastrointestinal bleeding is increased**

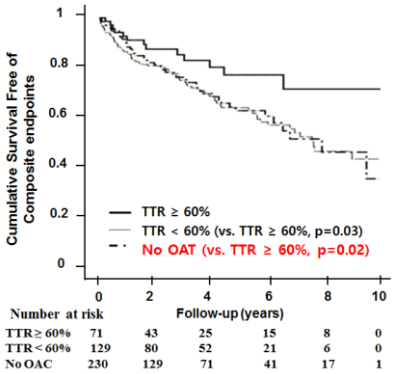
	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	*p*-value
Efficacy				
Ischaemic stroke	665/29,292	724/29,221	0.92 (0.83–1.02)	0.10
Haemorrhagic stroke	130/29,292	263/29,221	0.49 (0.38–0.64)	<0.0001
Myocardial infarction	413/29,292	432/29,221	0.97 (0.78–1.20)	0.77
All-cause mortality	2022/29,292	2245/29,221	0.90 (0.85–0.95)	0.0003
Safety				
Intracranial haemorrhage	204/29,287	425/29,211	0.48 (0.39–0.59)	<0.0001
Gastrointestinal bleeding	751/29,287	591/29,211	1.25 (1.01–1.55)	0.043

Ruff CT *et al*, *Lancet* 2014;383:955–962

High risk AF patients

Peptic Ulcer

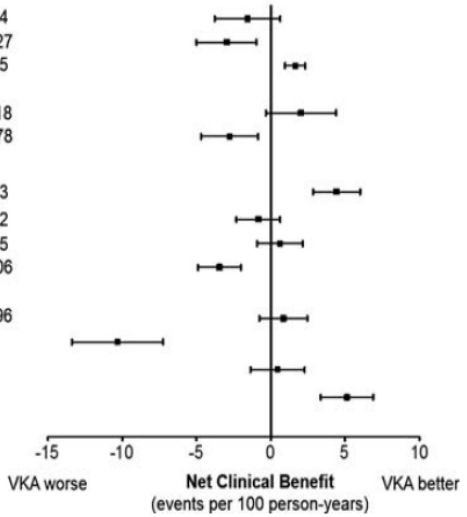




Lee SJ. Am J Cardiol 2012;110:373-377

- multicenter, retrospective analysis,
- clinical outcomes of 754 AF patients with a history of ulcer bleeding

Risk group (n)		No. of Patients VKA	No VKA
$CHADS_2 = 1$		36	74
$CHADS_2 = 2$		201	127
$CHADS_2 \geq 3$		221	95
HAS-BLED < 3		127	118
HAS-BLED ≥ 3		331	178
$CHADS_2 \geq 3$	HAS-BLED < 3	48	23
	HAS-BLED ≥ 3	173	72
$CHADS_2 < 3$	HAS-BLED < 3	79	95
	HAS-BLED ≥ 3	158	106
Overall		458	296
TTR < 55		109	
55 ≤ TTR < 65		224	
TTR ≥ 65		125	



Lee SJ, et al. Medicine. 2016;95:47

Dabigatran and GI bleeding

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

In RE-LY, dabigatran 150 mg twice daily was associated with a higher rate of MGIB compared with warfarin [RR 1.50], but the MGIB risk with dabigatran 110 mg twice daily was comparable with that of warfarin (RR 1.10).

Connolly S, at al. N Engl J Med 2009;361.

Dabigatran and GI bleeding

Table 4. Risks of Major, Intracranial, and Extracranial Bleeding With Dabigatran 110 Twice a Day, Dabigatran 150 mg Twice a Day, and Warfarin in Patients Aged <75 (n=10 855) and ≥75 (n=7258) Years

	Warfarin		Dabigatran 110 mg BID		Dabigatran 150 mg BID		Dabigatran 110 mg BID vs Warfarin (n=12 037)		Dabigatran 150 mg BID vs Warfarin (n=12 098)		Dabigatran 150 mg BID vs Dabigatran 110 mg BID (n=12 091)	
	n	%/y	n	%/y	n	%/y	RR	*P**	RR	*P**	RR	*P**
Stroke/systemic embolism												
Age <75 y	101	1.43	96	1.32	65	0.90	0.93 (0.70–1.22)		0.63 (0.46–0.86)		0.68 (0.50–0.94)	
Age ≥75 y	101	2.14	87	1.89	69	1.43	0.88 (0.66–1.17)	0.81	0.67 (0.49–0.90)	0.81	0.76 (0.55–1.04)	0.65
Major bleeding												
Age <75 y	215	3.04	138	1.89	153	2.12	0.62 (0.50–0.77)		0.70 (0.57–0.86)		1.12 (0.89–1.41)	
Age ≥75 y	206	4.37	204	4.43	246	5.10	1.01 (0.83–1.23)	<0.001	1.18 (0.98–1.42)	<0.001	1.17 (0.97–1.40)	0.80
Intracranial bleeding												
Age <75 y	43	0.61	10	0.14	19	0.26	0.22 (0.11–0.45)		0.43 (0.25–0.74)		1.92 (0.89–4.13)	
Age≥75 y	47	1.00	17	0.37	20	0.41	0.37 (0.21–0.64)	0.28	0.42 (0.25–0.70)	0.91	1.13 (0.59–2.15)	0.29
Extracranial bleeding												
Age <75 y	173	2.44	128	1.76	138	1.91	0.72 (0.57–0.90)		0.78 (0.63–0.98)		1.09 (0.86–1.39)	
Age≥75 y	162	3.44	189	4.10	226	4.68	1.20 (0.97–1.48)	0.001	1.39 (1.13–1.70)	<0.001	1.15 (0.95–1.40)	0.72
Gastrointestinal bleeding												
Age <75 y	73	1.03	61	0.84	88	1.22	0.82 (0.58–1.15)		1.19 (0.87–1.63)		1.46 (1.06–2.03)	
Age≥75 y	75	1.59	101	2.19	135	2.80	1.39 (1.03–1.98)	0.02	1.79 (1.35–2.37)	0.06	1.29 (0.99–1.66)	0.54
Nongastrointestinal extracranial bleeding												
Age <75 y	110	1.55	76	1.04	57	0.79	0.67 (0.50–0.90)		0.51 (0.37–0.70)		0.76 (0.54–1.07)	
Age ≥75 y	92	1.95	92	2.00	109	2.26	1.02 (0.76–1.36)	0.04	1.16 (0.88–1.53)	<0.001	1.14 (0.86–1.50)	0.07

An increased RR of MGIB with dabigatran was seen only in patients aged ≥75 years

Eikelboom J, et al. Circulation. 2011;123:2363-2372.

The US Center for Medicare and Medicaid Services (CMS) database ; Dabigatran

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	No. of Events		Incidence Rate per 1000 Person-Years		Adjusted Hazard Ratio	
	Dabigatran	Warfarin	Dabigatran	Warfarin	(95% CI)	*P* Value
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67–0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88–1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14–1.44)	<0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26–0.46)	<0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24–0.47)	<0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78–1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92–1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77–0.96)	0.006

A propensity-matched analysis from the US CMS database showed an increased risk of MGIB in patients receiving dabigatran (pooled data from 150 to 75mg twice daily doses) compared with warfarin (HR 1.28).

Graham D, et al. Circulation. 2015;131:157-164.

The US Center for Medicare and Medicaid Services (CMS) database ; Dabigatran

	Age Group (n)	Men, Hazard Ratio (95% CI)	Women, Hazard Ratio (95% CI)
Ischemic stroke			
	65–74 (55 761)	0.69 (0.42–1.14)	0.81 (0.51–1.31)
	75–84 (57 345)	0.98 (0.64–1.51)	0.89 (0.64–1.26)
	≥85 (21 308)	0.89 (0.41–1.90)	0.60 (0.40–0.91)
Intracranial hemorrhage			
	65–74 (55 761)	0.32 (0.15–0.68)	0.13 (0.04–0.44)
	75–84 (57 345)	0.27 (0.14–0.50)	0.59 (0.35–0.98)
	≥85 (21 308)	0.51 (0.18–1.48)	0.26 (0.12–0.56)
Major gastrointestinal bleeding			
	65–74 (55 761)	0.83 (0.60–1.14)	0.99 (0.72–1.37)
	75–84 (57 345)	1.02 (0.79–1.31)	1.50 (1.20–1.88)
	≥85 (21 308)	1.55 (1.04–2.32)	2.18 (1.61–2.97)
Mortality			
	65–74 (55 761)	0.81 (0.62–1.05)	0.72 (0.52–0.99)
	75–84 (57 345)	0.73 (0.58–0.92)	0.82 (0.65–1.03)
	≥85 (21 308)	0.92 (0.64–1.33)	1.24 (0.96–1.60)

Graham D, et al. Circulation. 2015;131:157-164.

The US Center for Medicare and Medicaid Services (CMS) database ; Dabigatran

Table 4. Effect of Daily Dose of Dabigatran on Risk of Ischemic Stroke, Major Gastrointestinal Bleeding, Intracranial Hemorrhage, and Mortality Compared With Treatment With Warfarin for Nonvalvular Atrial Fibrillation*

	Ischemic Stroke, Hazard Ratio (95% CI)	Major Gastrointestinal Bleed, Hazard Ratio (95% CI)	Intracranial Hemorrhage, Hazard Ratio (95% CI)	Mortality, Hazard Ratio (95% CI)
75 mg twice daily (n=10 522)	0.88 (0.60–1.27)	1.01 (0.78–1.31)	0.46 (0.26–0.81)	0.95 (0.78–1.16)
150 mg twice daily (n=56 576)	0.70 (0.57–0.85)	1.51 (1.32–1.73)	0.30 (0.21–0.42)	0.76 (0.67–0.86)

Graham D, et al. Circulation. 2015;131:157-164.

Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study

the IMS Health LifeLink Health Plan Claims Database (USA)

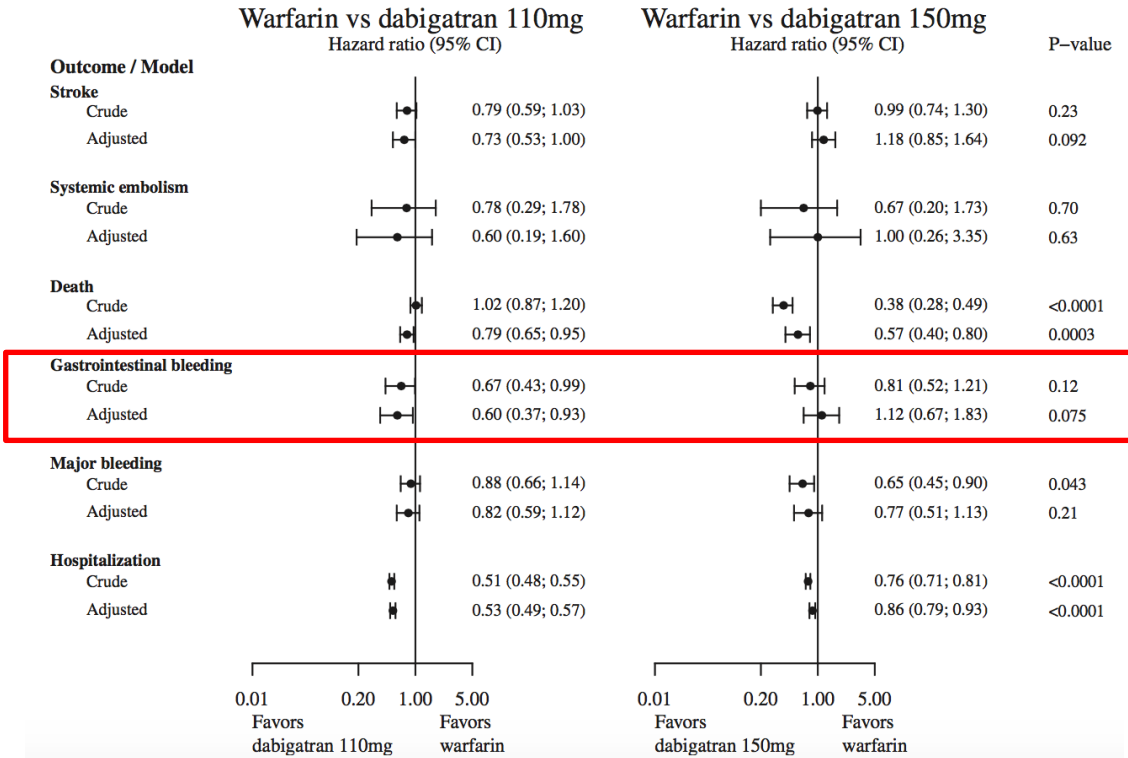
Table 2 | Multivariable association between novel oral anticoagulant use and gastrointestinal bleeding

Analysis	Dabigatran (reference group: warfarin)	Rivaroxaban (reference group: warfarin)
All patients:	(n=44 514)	(n=41 256)
Crude hazard ratio* (95% CI)	1.20 (0.96 to 1.52)	0.95 (0.31 to 2.94)
Adjusted hazard ratio† (95% CI)	1.21 (0.96 to 1.53)	0.98 (0.36 to 2.69)
Patients aged under 65 years:	(n=34 038)	(n=32 099)
Crude hazard ratio* (95% CI)	1.33 (0.98 to 1.80)	1.08 (0.27 to 4.41)
Adjusted hazard ratio† (95% CI)	1.34 (0.98 to 1.83)	1.03 (0.33 to 3.18)
Patients aged over 65 years:	(n=10 476)	(n=9157)
Crude hazard ratio* (95% CI)	1.07 (0.75 to 1.52)	0.69 (0.10 to 4.68)
Adjusted hazard ratio† (95% CI)	1.07 (0.75 to 1.53)	0.62 (0.18 to 2.08)

Chang H, et al. BMJ 2015;350:h1585

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With AF

the Danish Registry of Medicinal Product Statistics,



Larsen T, et al. J Am Coll Cardiol 2013;61:2264–73

Bleeding Events Among New Starters and Switchers to Dabigatran Compared with Warfarin in AF: Danish registry

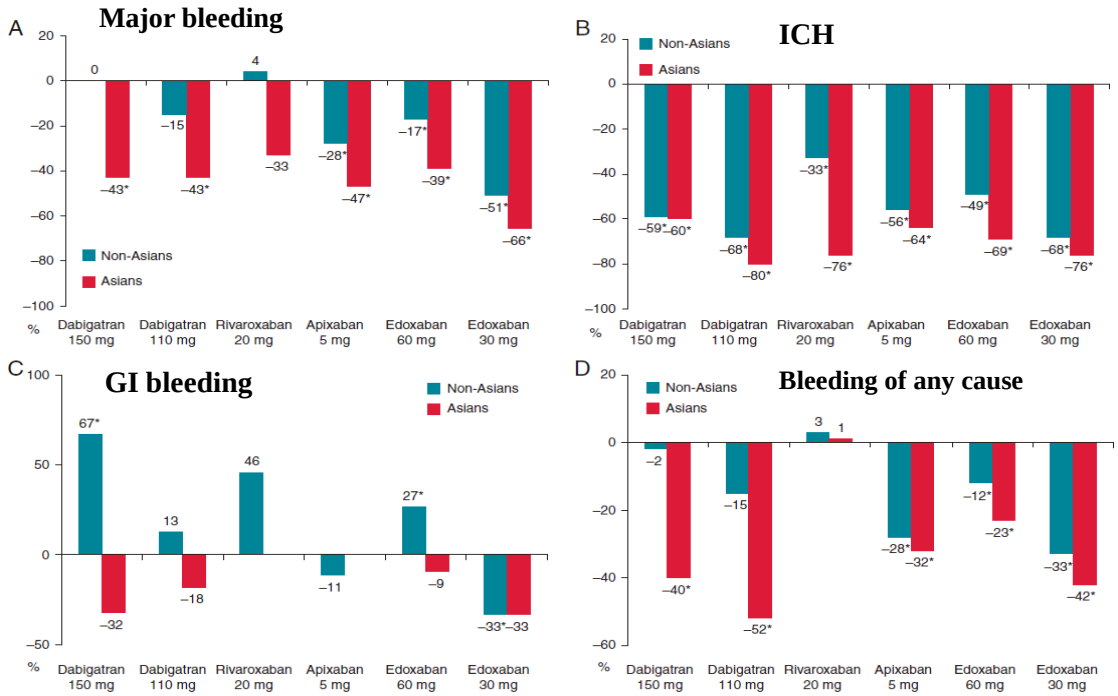
Table 2 Crude Event Rates and Hazard Ratios Across All 6 Combinations of Treatment and Vitamin K Antagonist—Experience Stratum (Naïve or Experienced)

	No. of Events		Events per 100 Person-Years		Adjusted* HR (95% CI)		*P* Value for Interaction†
	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced	
Primary end points							
Any bleeding							.01
Warfarin	663	379	5.1	3.8	1.00 (reference)	0.71 (0.63-0.82)	
Dabigatran 110 mg	123	108	4.5	5.1	0.72 (0.59-0.88)	0.81 (0.66-1.00)	
Dabigatran 150 mg	111	76	2.9	2.8	0.67 (0.55-0.83)	0.59 (0.46-0.75)	
Major bleeding							.15
Warfarin	479	265	3.7	2.6	1.00 (reference)	0.68 (0.58-0.80)	
Dabigatran 110 mg	102	74	3.7	3.5	0.91 (0.73-1.14)	0.83 (0.64-1.07)	
Dabigatran 150 mg	86	59	2.2	2.1	0.67 (0.53-0.85)	0.59 (0.45-0.78)	
Secondary end points							
Fatal bleeding							.02
Warfarin	72	37	0.54	0.36	1.00 (reference)	0.59 (0.39-0.91)	
Dabigatran 110 mg	13	20	0.46	0.92	0.48 (0.25-0.87)	0.91 (0.54-1.53)	
Dabigatran 150 mg	8	8	0.21	0.29	0.75 (0.35-1.61)	0.81 (0.38-1.75)	
Gastrointestinal bleeding							.05
Warfarin	78	52	0.58	0.51	1.00 (reference)	0.91 (0.62-1.32)	
Dabigatran 110 mg	12	21	0.42	0.97	0.53 (0.28-0.98)	1.22 (0.73-2.03)	
Dabigatran 150 mg	19	12	0.49	0.43	1.37 (0.81-2.31)	1.03 (0.54-1.93)	
Intracranial bleeding							.11
Warfarin	131	73	0.98	0.71	1.00 (reference)	0.72 (0.53-0.98)	
Dabigatran 110 mg	13	15	0.46	0.69	0.31 (0.17-0.55)	0.49 (0.28-0.86)	
Dabigatran 150 mg	9	8	0.23	0.29	0.32 (0.16-0.63)	0.38 (0.18-0.78)	

the Danish Registry of Medicinal Product Statistics

Larsen T, et al. Am J Med 2014;127:650-656

Relative risk reduction in four major safety endpoints in Asians and non-Asians



Chiang C et al. Europace2015;17:ii31

Prevention of Dabigatran-Related GI Bleeding With Gastroprotective Agents: A Population-Based Study

a retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority.

Table 4. Stratification Into Different Use of Gastroprotective Agents

	Overall[a]	H2RA alone	PPI alone	Both H2RA and PPI[b]
All users, n (%)	3401	2004	923	474
Continuous users[c]	2423 (71.2)	1393 (69.5)	660 (71.5)	370 (78.1)
Infrequent users[c]	978 (28.8)	611 (30.5)	263 (28.5)	104 (21.9)
Main model, incidence rate ratios (95% CI)				
All users	0.52 (0.35–0.77)	0.61 (0.40–0.94)	0.53 (0.31–0.91)	0.15 (0.06–0.39)
Continuous users[c]	0.51 (0.34–0.77)	0.62 (0.40–0.97)	0.48 (0.26–0.87)	0.18 (0.07–0.47)
Infrequent users[c]	0.54 (0.31–0.96)	0.59 (0.30–1.15)	0.76 (0.32–1.79)	[d]
Time-to-event analysis, hazard rate ratios (95% CI)				
All users	0.57 (0.38–0.85)	0.66 (0.43–1.01)	0.57 (0.34–0.97)	0.19 (0.07–0.49)
Continuous users[c]	0.57 (0.38–0.87)	0.68 (0.43–1.06)	0.53 (0.29–0.95)	0.23 (0.09–0.60)
Infrequent users[c]	0.57 (0.32–1.00)	0.61 (0.31–1.19)	0.74 (0.32–1.75)	[d]

Chan E, et al. Gastroenterology 2015;149:586–595

Factors Associated With Major Bleeding Events Insights From the ROCKET AF Trial

	Rivaroxaban (n = 7,111)	Warfarin (n = 7,125)
Major bleeding or nonmajor clinically relevant bleeding	1,475 (20.7)	1,449 (20.3)
GI (upper, lower, and rectal)*	394 (5.5)	290 (4.1)
Intracranial†	55 (0.77)	84 (1.18)
Intraparenchymal†	37 (0.52)	56 (0.79)
Nontraumatic†	33 (0.46)	54 (0.76)
Traumatic	4 (0.06)	2 (0.03)
Intraventricular‡	13 (0.18)	30 (0.42)
Subdural hematoma†	14 (0.20)	27 (0.38)
Subarachnoid	7 (0.10)	14 (0.20)
Epidural hematoma	0	1 (0.01)

In ROCKET AF, patients receiving rivaroxaban 20 mg once daily had a significantly higher risk of MGIB than did those on warfarin (3.2 vs. 2.2%; $P < 0.001$),

Goodman SG, et al. J Am Coll Cardiol 2014;63:891–900.

Bleeding Sites According to Age Category; From the ROCKET AF Trial

Table 5. Bleeding Sites According to Age Category and Treatment Allocation

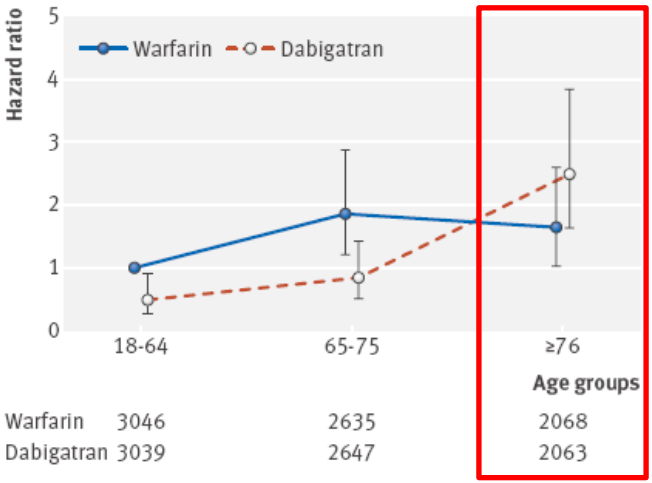
	Age ≥75 y			Age <75 y		
	Rivaroxaban (n=3111)*	Warfarin (n=3104)*	*P* Value	Rivaroxaban (n=4000)*	Warfarin (n=4021)*	*P* Value
Gastrointestinal (upper, lower, and rectal)	2.81	1.66	0.0002	1.41	0.94	0.0136
Intracranial	0.66	0.83	0.3531	0.37	0.68	0.0156
Intraparenchymal	0.41	0.49	0.5565	0.28	0.50	0.0441
Nontraumatic	0.34	0.47	0.3437	0.26	0.48	0.0402
Traumatic	0.06	0.02	0.3348	0.02	0.02	0.9947
Intraventricular	0.19	0.36	0.1288	0.06	0.20	0.0422
Subdural hematoma	0.23	0.32	0.4347	0.05	0.18	0.0343
Subarachnoid	0.11	0.19	0.2972	0.03	0.08	0.2836
Epidural hematoma	0.00	0.02	…	0.00	0.00	…
Macroscopic hematuria	0.32	0.19	0.2213	0.17	0.18	0.8687
Bleeding associated with noncardiac surgery	0.26	0.36	0.3575	0.11	0.14	0.6408
Intraocular/retinal	0.17	0.25	0.3811	0.14	0.18	0.5432
Intra-articular	0.21	0.28	0.5495	0.09	0.12	0.6094
Epistaxis	0.11	0.23	0.2292	0.11	0.05	0.2100

*Event rates per 100 patient-years of follow-up.

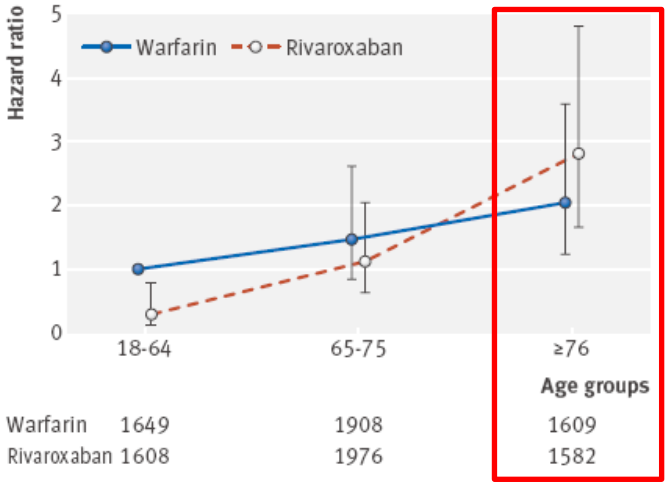
Halperin J, et al. Circulation. 2014;130:138-146

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

Dabigatran vs. Warfarin



Rivaroxaban vs. Warfarin



Optum Labs Data Warehouse, a large database including administrative claims data on privately insured and Medicare Advantage enrollees.

Abraham N, et al. BMJ 2015;350:h1857

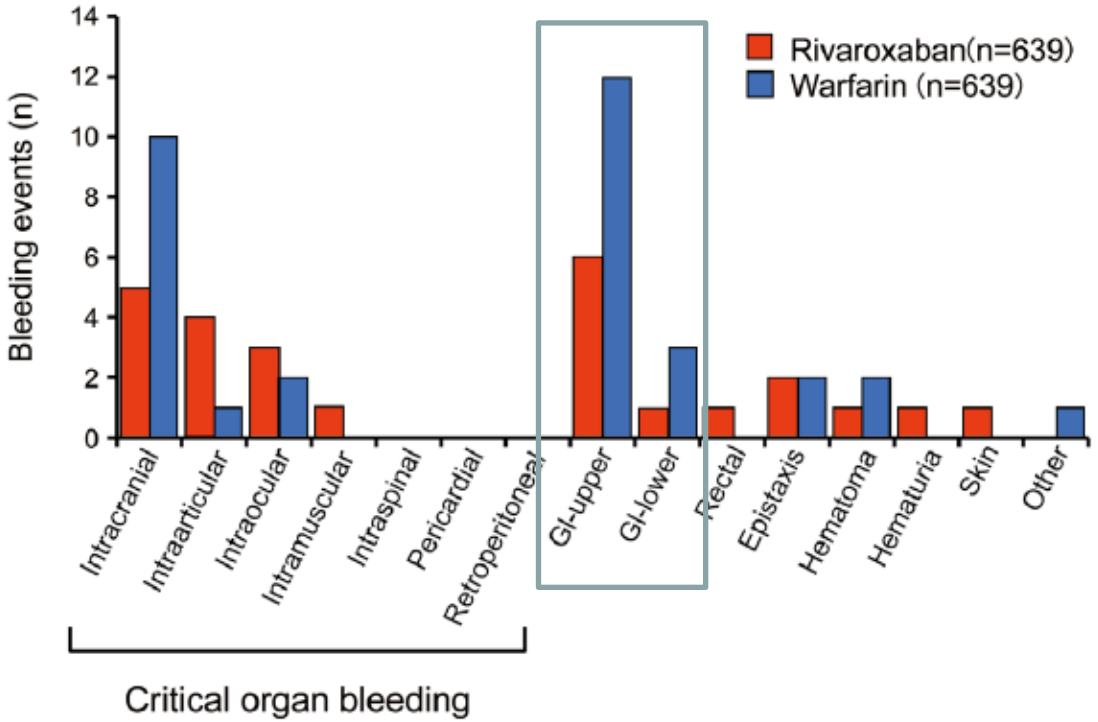
Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKETAF trial

Table 2 Location of major bleeds by randomized treatment[a]

Characteristic	Rivaroxaban (n = 431)	Warfarin (n = 409)
Number of major bleeds[b]		
1	361 (91.4%)	359 (93.5%)
2	32 (8.1%)	25 (6.5%)
>2	2 (0.5%)	0 (0.0%)
Bleeding details		
Bleeding associated with cardiac surgery (including CABG)	0 (0.0%)	2 (0.5%)
Bleeding associated with non-cardiac surgery	19 (4.4%)	27 (6.6%)
Epistaxis	14 (3.2%)	14 (3.4%)
GI: Upper (haematemesis or melena)	164 (38.1%)	105 (25.7%)
GI: Lower	51 (11.8%)	33 (8.1%)
Gingival	1 (0.2%)	2 (0.5%)
Haematoma	13 (3.0%)	26 (6.4%)
Haemoptysis	5 (1.2%)	4 (1.0%)
Increased or prolonged menstrual or abnormal vaginal bleeding	3 (0.7%)	1 (0.2%)
Intra-articular	16 (3.7%)	21 (5.1%)
Intracranial	55 (12.8%)	84 (20.5%)
Intramuscular (with compartment syndrome)	2 (0.5%)	1 (0.2%)
Intramuscular (without compartment syndrome)	2 (0.5%)	4 (1.0%)
Intraocular/retinal	19 (4.4%)	27 (6.6%)
Macroscopic (gross) haematuria	27 (6.3%)	21 (5.1%)
Pericardial	0 (0.0%)	1 (0.2%)
Puncture site	2 (0.5%)	4 (1.0%)
Rectal	28 (6.5%)	8 (2.0%)
Retroperitoneal	1 (0.2%)	3 (0.7%)
Skin (ecchymosis other than instrumented site)	2 (0.5%)	3 (0.7%)
Subconjunctival or other ocular	0 (0.0%)	1 (0.2%)
Other	7 (1.6%)	19 (4.6%)

Piccini J, et al. Eur Heart J (2014) 35, 1873–1880.

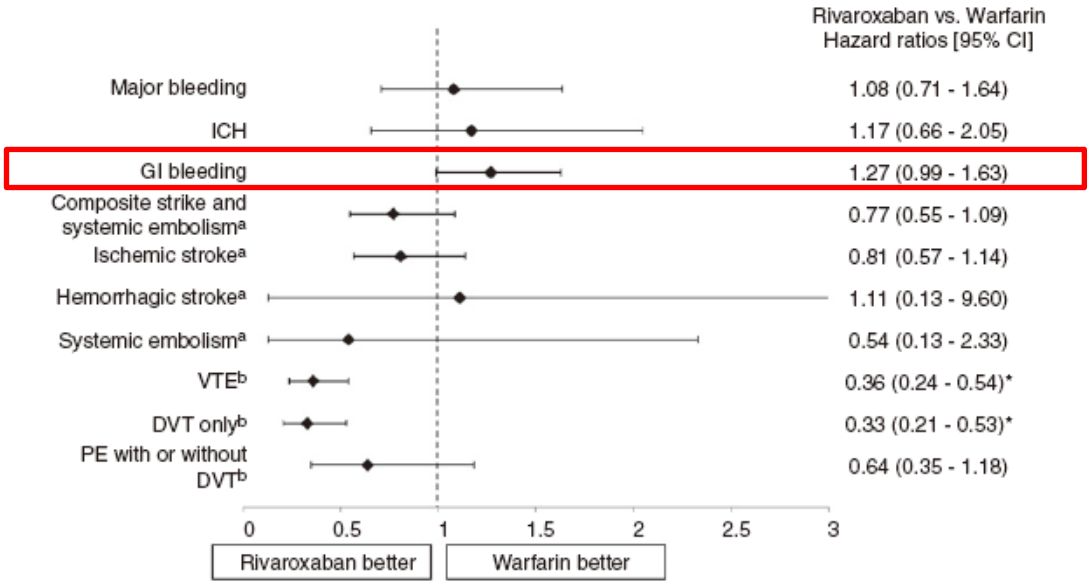
Rivaroxaban vs. Warfarin in Japanese Patients With Atrial Fibrillation – The J-ROCKET AF Study –



Hori M, et al. *Circ J* 2012; **76:** 2104 – 2111.

Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients

Healthcare claims from Symphony Health Solutions' Patient Transactional Datasets from May 2011 to July 2012



ICH: intracranial hemorrhage; GI: gastrointestinal; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.
*Statistically significant at 0.05 level.
[a]Event identified during a hospitalization or emergency department visit.
[b]Event identified during a hospitalization, an emergency department visit, or an outpatient visit (with a 6 month washout).

Laliberté F, et al. Curr Med Res Opin 2014; 30:1317–25

Apixaban versus Warfarin in Patients with Atrial Fibrillation : ARISTOTLE

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

Granger C, et al. N Engl J Med 2011;365:981-92.

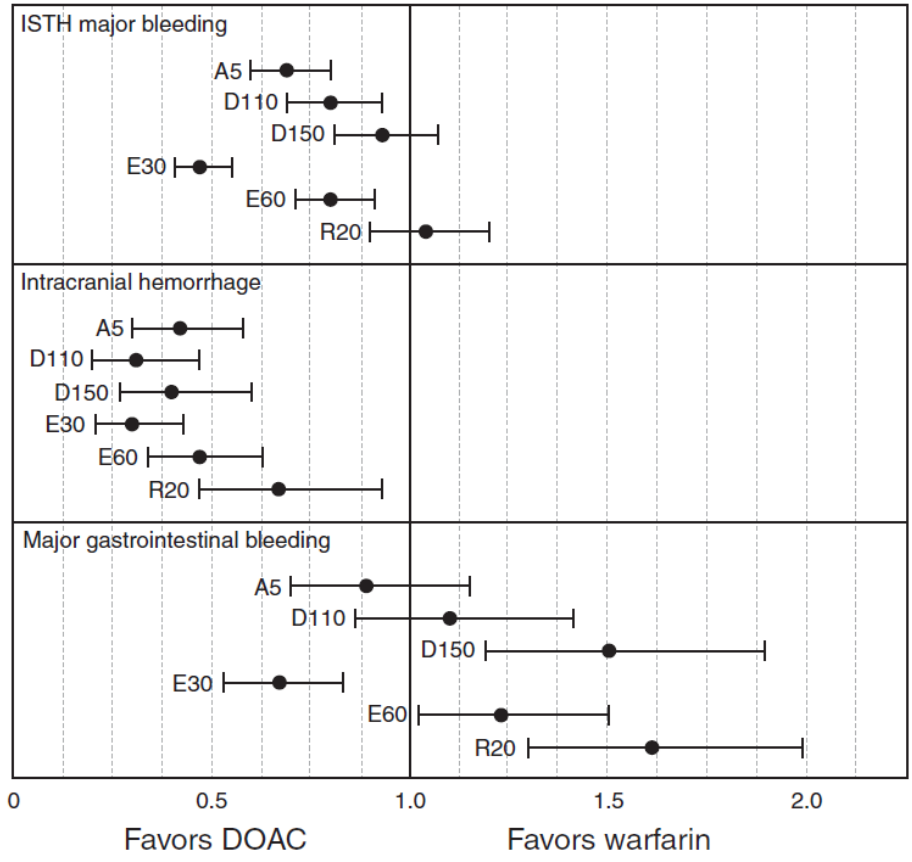
Edoxaban versus Warfarin in Patients with Atrial Fibrillation : ENGAGE-TIMI 48

Table 3. Safety and Net Clinical End Points.*

Outcome	Warfarin (N=7012)		High-Dose Edoxaban (N=7012)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7002)		Low-Dose Edoxaban vs. Warfarin	
					Hazard Ratio (95% CI)	P Value			Hazard Ratio (95% CI)	P Value
	no. of patients with event	*% of patients/yr*	*no. of patients with event*	*% of patients/yr*			*no. of patients with event*	*% of patients/yr*		
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Fatal	59	0.38	32	0.21	0.55 (0.36–0.84)	0.006	21	0.13	0.35 (0.21–0.57)	<0.001
Bleeding into a critical organ or area	211	1.36	108	0.70	0.51 (0.41–0.65)	<0.001	69	0.44	0.32 (0.24–0.42)	<0.001
Overt bleeding with blood loss of ≥2 g/dl	327	2.13	317	2.08	0.98 (0.84–1.14)	0.78	187	1.19	0.56 (0.47–0.67)	<0.001
Any intracranial bleeding	132	0.85	61	0.39	0.47 (0.34–0.63)	<0.001	41	0.26	0.30 (0.21–0.43)	<0.001
Fatal intracranial bleeding	42	0.27	24	0.15	0.58 (0.35–0.95)	0.03	12	0.08	0.28 (0.15–0.53)	<0.001
Gastrointestinal bleeding	190	1.23	232	1.51	1.23 (1.02–1.50)	0.03	129	0.82	0.67 (0.53–0.83)	<0.001
Upper gastrointestinal tract	111	0.71	140	0.91	1.27 (0.99–1.63)	0.06	88	0.56	0.78 (0.59–1.03)	0.08
Lower gastrointestinal tract	81	0.52	96	0.62	1.20 (0.89–1.61)	0.23	44	0.28	0.54 (0.37–0.77)	<0.001
Bleeding in other location	211	1.37	131	0.85	0.62 (0.50–0.78)	<0.001	87	0.55	0.40 (0.31–0.52)	<0.001
Bleeding during transition to open-label oral anticoagulation therapy										
Day 1–14	6	—	4	—	—	—	5	—	—	—
Day 15–30	5	—	6	—	—	—	13	—	—	—

Giugliano RP, et al. N Engl J Med 2013;369:2093–2104.

Safety of NOACs
-GI Bleeding



Risk Ratio (95% CI)

0.89 (0.70 - 1.15)

1.08 (0.85 – 1.38)

1.48 (1.18 - 1.85)

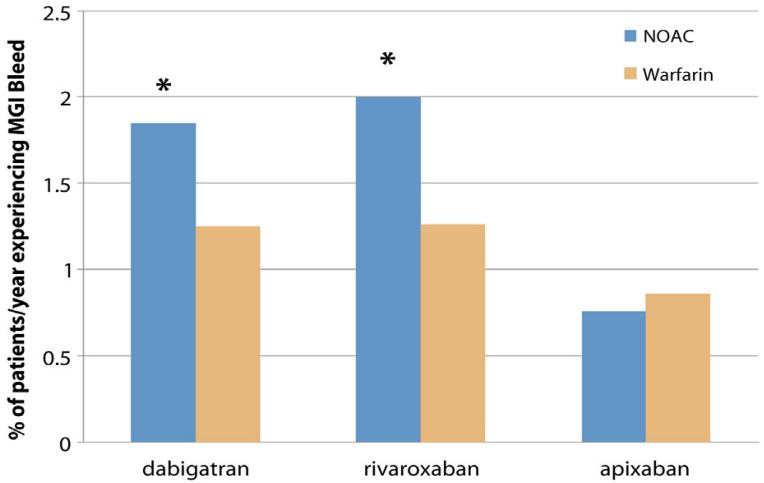
0.67 (0.53– 0.83)

1.23 (1.02– 1.50)

1.61 (1.30– 1.99)

GI Bleeding of NOAC in RCTs Pathophysiology

- **A First hypothesis – direct injury to the GI tract**
  - **Tartaric acid in dabigatran capsules may be responsible; however, rivaroxaban also promotes GI bleeding, and Aggrenox (Boehringer Ingelheim, Germany), which also contains tartaric acid, does not.**
  - **Rivaroxaban is dosed once daily, thereby leading to higher peak-to-trough anticoagulant activity than apixaban, which is dosed twice daily**



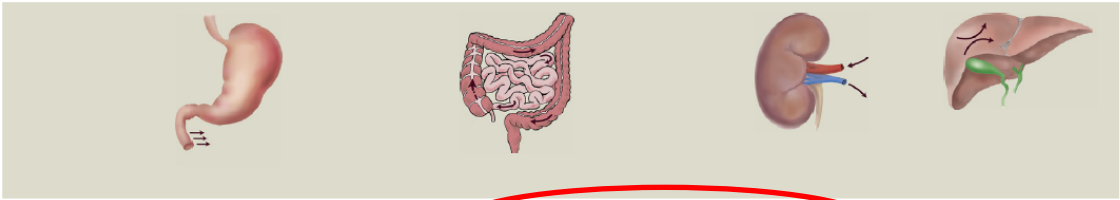
*** Statistically significant increased rate of gastrointestinal bleeding compared to warfarin**

Desai et al. Novel oral anticoagulants in gastroenterology. GASTROINTESTINAL ENDOSCOPY. 2013 Vol 78, No 2.

GI Bleeding of NOAC - Pathophysiology

- **A second hypothesis**
  - **Non-absorbed, active anticoagulant drug within the GI tract lumen promotes GI bleeding (eg, from vulnerable mucosal erosions or angiectasias). The absorption of warfarin in contrast is >95%, and intraluminal drug has no anticoagulant activity.**

TABLE 2. Comparison of the absorption and elimination of warfarin, apixaban, dabigatran, and rivaroxaban



	Bioavailability	Active anticoagulant present in GI tract	Renal excretion	Hepatic metabolism
Warfarin	100%	None	None	High
Dabigatran	7%	High	High	Low
Rivaroxaban	66%	Moderate	Moderate	Moderate
Apixaban	50%	Moderate	Moderate	Moderate

Desai et al. Novel oral anticoagulants in gastroenterology. GASTROINTESTINAL ENDOSCOPY. 2013 Vol 78. No 2.

Clinical outcome according to NOAC: Yonsei

Total (n=5702)	Warfarin (n =4990)	NOAC (n = 5702)	p-value	Dabigatran	Apixaban	Ribaroxaban
MACE, n (%)	63 (1.3)	29 (0.5)	<0.001	7 (0.4)	14 (0.7)	8 (0.5)
%/year	0.96	0.53	0.001	0.38	0.77	0.50
Stroke, n (%)	52 (1.0)	19 (0.3)	<0.001	5 (0.3)	8 (0.4)	6 (0.4)
%/year	0.79	0.35	<0.001	0.27	0.44	0.38
Systemic embolism	9 (0.2)	2 (0.04)	0.042	0 (0)	1 (0.1)	1 (0.1)
%/year	0.14	0.04	0.051	0	0.05	0.06
Major bleeding	96 (1.9)	41 (0.7)	<0.001	10 (0.6)	11 (0.6)	19 (1.2)
%/year	1.47	0.75	<0.001	0.54	0.60	1.20
GI system	50 (1.0)	25 (0.4)	0.001	5 (0.3)	9 (0.5)	10 (0.6)
%/year	0.77	0.46	0.013	0.27	0.49	0.63
CNS system	33 (0.7)	12 (0.2)	0.001	4 (0.2)	1 (0.1)	7 (0.4)
%/year	0.51	0.22	0.004	0.22	0.05	0.44
Follow up (median, day)	362 (100, 752)	286 (105, 550)	<0.001	298 (106, 580)	305 (107, 560)	314 (102, 570)

Kim K, et al. unpublished

GI Bleeding of NOAC
- Risk factors of major GI bleeding

- **Dabigaran-associated GI bleeding**
  - **Decreased kidney function**
  - **African-American race**
  - **Multiple co-morbidities**
  - **Upper GI symptom (dyspepsia): double 3.2 % vs. 1.3 % / year**
  - **One antiplatelet: HR 1.81, 95 % CI 1.46 – 2.24**
  - **Two antiplatelets: HR 2.16, 95 % CI 1.34 – 3.47**

- **Rivaroxaban-associated GI bleeding**
  - **Concurrent use of antiplatelet agent**
  - **Decreased creatinine clearance**
  - **Hx of previous GI hemorrhage**

- **Apixaban-associated GI bleeding**
  - **Aspirin/NSAID use**
  - **Creatinine clearance < 85 ml/min**
  - **Prior episode of bleeding**

Desai et al. GI Bleeding in AF Patients Taking DOACs. Am J Gastroenterol Suppl 2016; 3:13 – 21

Take Home Message (1)

- **First choice**
  - **For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used**
- **Second choice**
  - **Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily**
- **Comments**
  - **GI bleeding, even in the setting of anticoagulation, does usually not cause death or permanent major disability. Thus, the choice of OAC should be driven mainly by stroke prevention considerations.**
  - **The label 'high risk of GI bleeding' is imprecise. For example, patients with H. pylori-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated.**

Diener H, et al. Eur Heart J 2017;38:860-868

Take Home Message (1)

- **Comments**
  - **The GI bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.**
  - **As with warfarin, NOAC agents should be restarted as soon as deemed safe to do so once GI bleeding has been controlled.**
  - **The gastrointestinal bleeding risk of dabigatran and edoxaban are dose-dependent.**
  - **The increased GI bleeding risk of dabigatran and rivaroxaban are most evident in patients ≥75 years old.**
  - **Gastrointestinal tract cancer screening and surveillance strategies (e.g. colonoscopy) increase early detection of occult tumours and may thereby reduce the incidence of neoplasm-associated GI bleeding in patients receiving OACs. Age-appropriate colorectal cancer screening should be undertaken prior to initiation of OAC.**

Diener H, et al. Eur Heart J 2017;38:860-868

경청해주셔서 감사합니다!

GI Bleeding of NOAC in RCTs
Major GI bleeding - Distribution

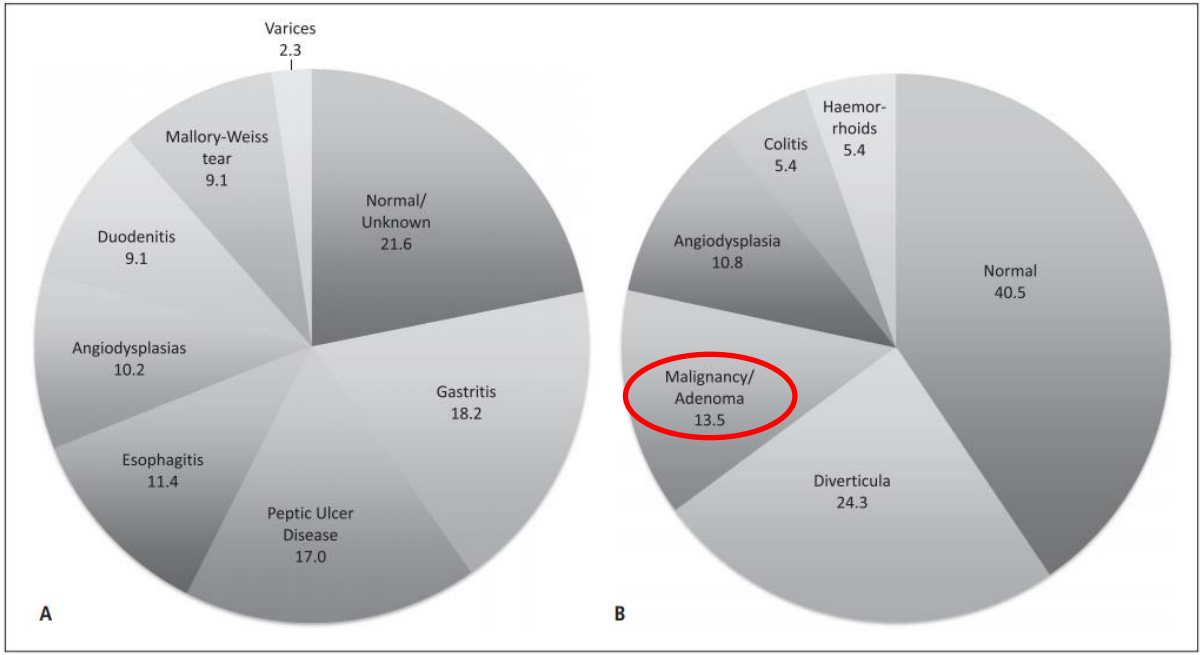
- **Major GI bleeding associated with VKAs, aspirin, and NSAIDs:**
  - **preponderantly from the upper GI tract.**
- **Major GI bleeding associated with dabigatran :**
  - **more commonly located distal to the Ligament of Treitz.**
  - **In RE-LY, 47% of patients taking dabigatran have experienced lower GI bleeding. (25% in warfarin group)**
- **Major GI bleeding associated with rivaroxaban :**
  - **22 % of events were from the lower tract, and 30 % of events were from a rectal source**
  - **In PMS, 57 % of patients taking rivaroxaban were found to have a lower GI source**
- **Major GI bleeding associated with apixaban:**
  - **for upper vs. lower GI bleeds: 0.43 per 100 patient-years vs. 0.25 per 100 patient-years**

Desai et al. Novel oral anticoagulants in gastroenterology. GASTROINTESTINAL ENDOSCOPY. 2013 Vol 78, No 2.

GI Bleeding of anticoagulants - Endoscopic findings

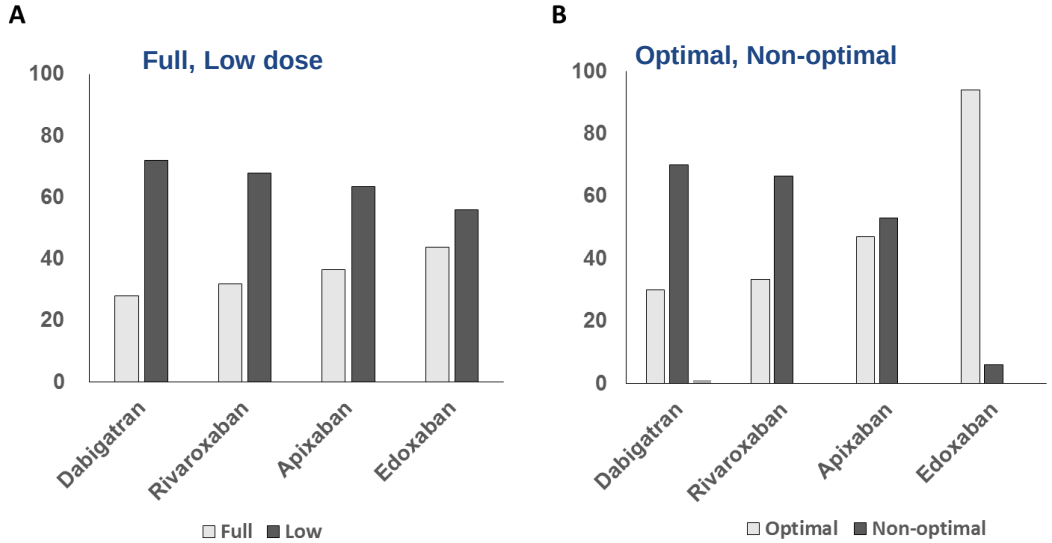
Upper GI

Lower GI



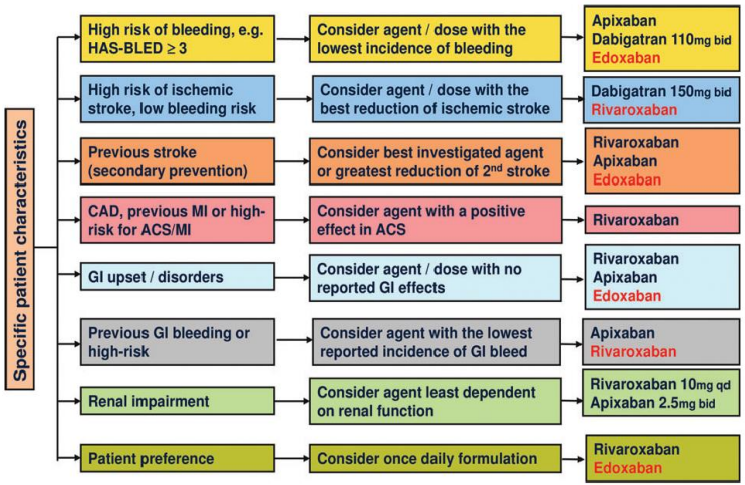
Desai et al. New oral anticoagulants and GI bleeding. Thromb Haemost 2013; 110: 205–212

Choice of NOAC for Korean patients with nonvalvular AF: analysis of a multicenter registry (COmparision study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; CODE-AF registry)

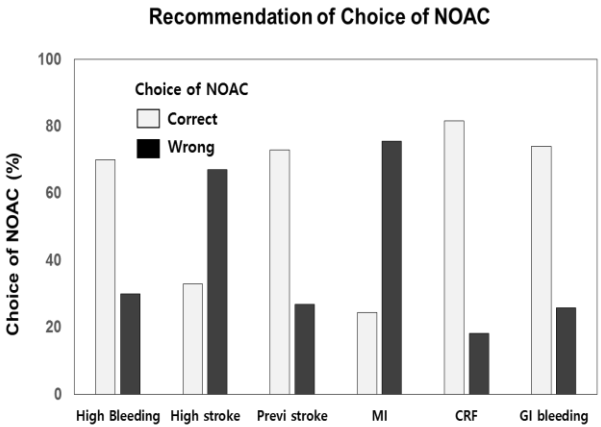


CODE-AF registry, Sung M, et al. (Unpublished)

Choice of NOAC for Korean patients with nonvalvular AF: analysis of a multicenter registry (COmparision study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; CODE-AF registry)



Okumura K, et al. Clin Cardiol 2017



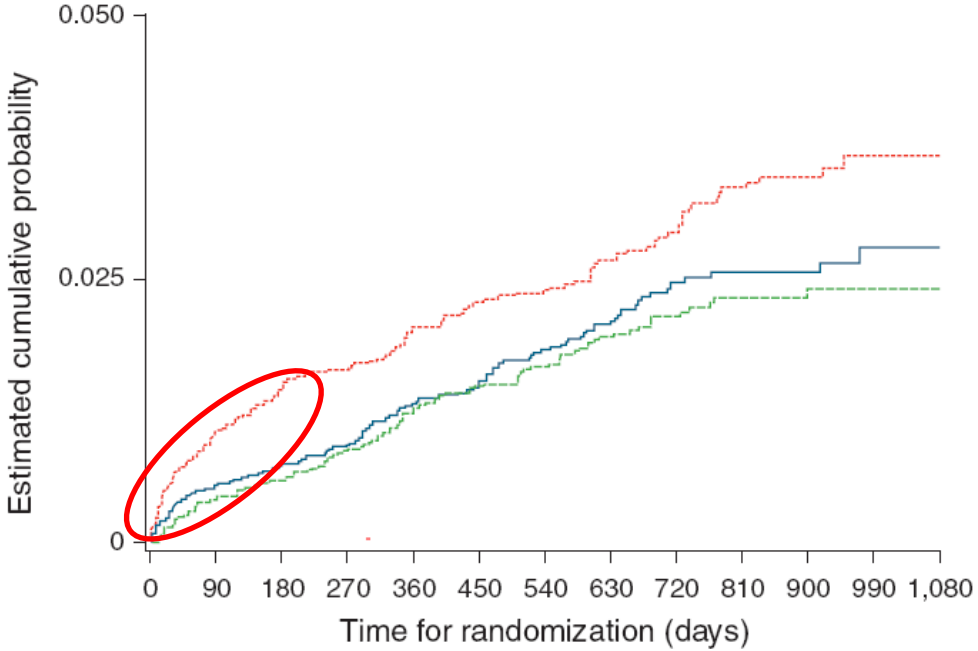
CODE-AF registry, Sung M, et al. (Unpublished)

GI Bleeding of Oral anticoagulants - General considerations

- Warfarin increases the risk of major GI bleeding approximately three-fold compared with placebo.
- The addition of aspirin or other anti-platelet agents to warfarin increases the risk of major GI bleeding approximately two-fold (compared with warfarin alone).
- Compared with warfarin, rivaroxaban and dabigatran 150, edoxaban 60mg increase the risk of major GI bleeding approximately 1.5 fold.
- Compared with warfarin, apixaban and dabigatran 110mg does not significantly alter the risk of major GI bleeding.

Desai et al. New oral anticoagulants and GI bleeding. Thromb Haemost 2013; 110: 205–212

GI Bleeding of NOAC
- Timing of major GI bleeding



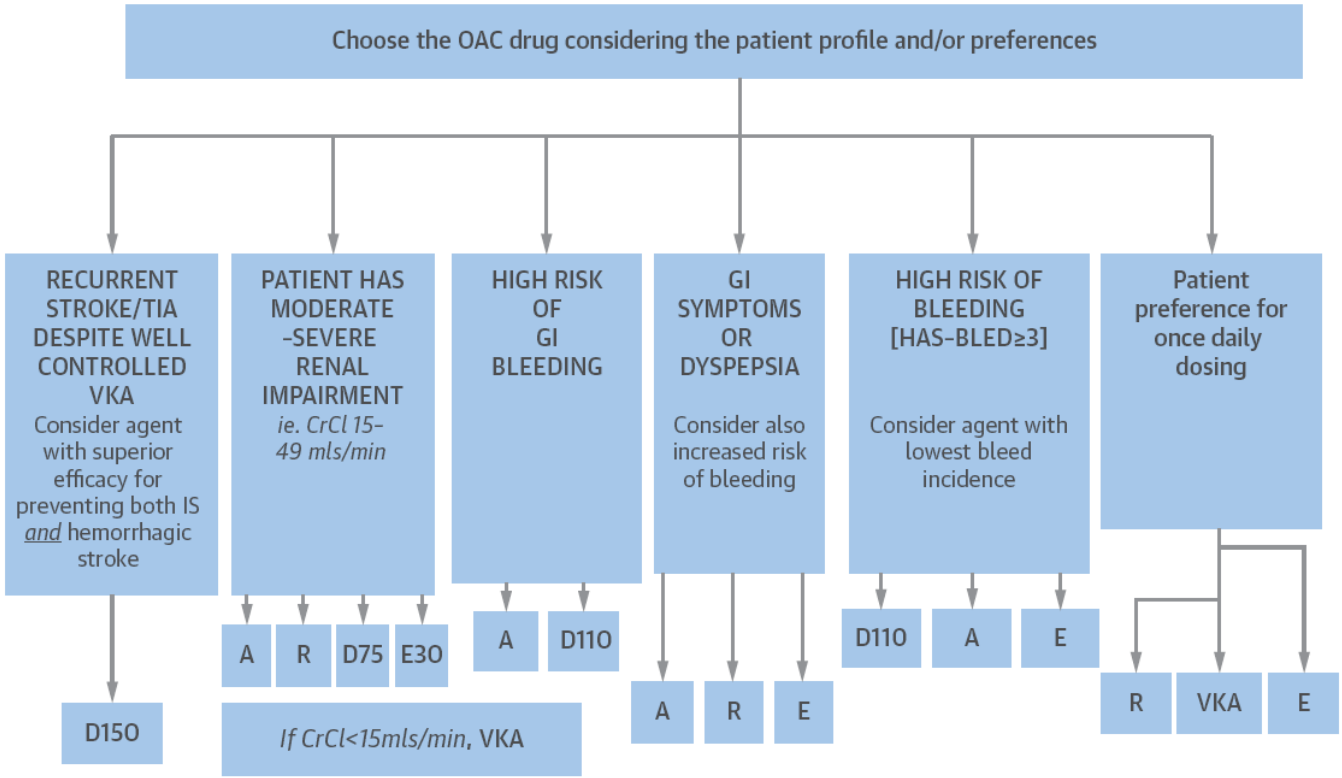
- event rate of major bleeding in the first 6 months
  : 2.04 per 100 patient-years (95 % CI 0.42 – 5.96);
- event rate of major bleeding during months 6 – 12
  : 0.78 per 100 patient-years (95 % CI 0.09 – 2.80)

Subjects at risk

DE 110 mg BID (*n*)	5,983	5,468	5,250	5,080	4,927	4,646	3,864	3,113	2,578	1,949	1,185	395	67
DE 150 mg BID (*n*)	6,059	5,476	5,237	5,066	4,915	4,638	3,877	3,119	2,596	1,937	1,172	369	76
Warfarin (*n*)	5,998	5,660	5,495	5,318	5,181	4,847	4,079	3,214	2,670	2,018	1,191	321	63

Desai et al. GI Bleeding in AF Patients Taking DOACs. Am J Gastroenterol Suppl 2016; 3:13 – 21

Selection of optimal oral anticoagulant



Gregory et al. J Ameri Coll Cardiol 2015

GI Bleeding of NOAC in RCTs - Much more bleeding risk in Real-World

- **Most trials used extensive exclusion criteria to enroll only those patients with a presumed low risk of GI bleeding complications attributable to anticoagulants.**

- **Almost 25%–40% of NOAC users are high-risk patients and the risk of hemorrhage can be as much as 3- to 15-fold increased than reported in RCTs.**

Table 3. Occurrence of exclusion criteria in patients with or without bleeding

	All patients with bleeding, cases	All patients without bleeding, controls	OR (95% CI)	AF patients with bleeding, cases	AF patients without bleeding, controls	OR (95% CI)	VTE patients with bleeding, cases	VTE patients without bleeding, controls	OR (95% CI)	ACS patients with bleeding, cases	ACS patients without bleeding, controls	OR (95% CI)
n	993	993	—	638	648	—	141	147	—	214	198	—
No exclusion criteria	597 (59.6%)	764 (76.9%)	—	374 (58.6%)	490 (75.6%)	—	105 (74.5%)	124 (84.4%)	—	118 (55.1%)	150 (75.8%)	—
1 exclusion criterion	205 (20.6%)	123 (12.4%)	2.9 (2.2-3.9)	121 (19.0%)	71 (15.2%)	3.3 (2.3-4.7)	20 (14.2%)	17 (11.6%)	1.8 (0.8-3.7)	64 (29.9%)	35 (17.7%)	3.1 (1.7-5.4)
2 exclusion criteria	174 (17.5%)	102 (10.3%)	3.8 (2.7-5.2)	128 (20.0%)	83 (12.8%)	4.5 (3.0-6.7)	15 (10.6%)	6 (4.1%)	4.2 (1.5-12.3)	31(14.5%)	13 (6.6%)	3.9 (1.8-8.2)
More than 2 exclusion criteria	17 (1.7%)	4 (0.4%)	14.9 (4.7-46)	15 (2.4%)	4 (0.6%)	20.6 (6.2-68.6)	1 (0.7%)	0 (0%)	—	1 (0.5%)	0 (0%)	—

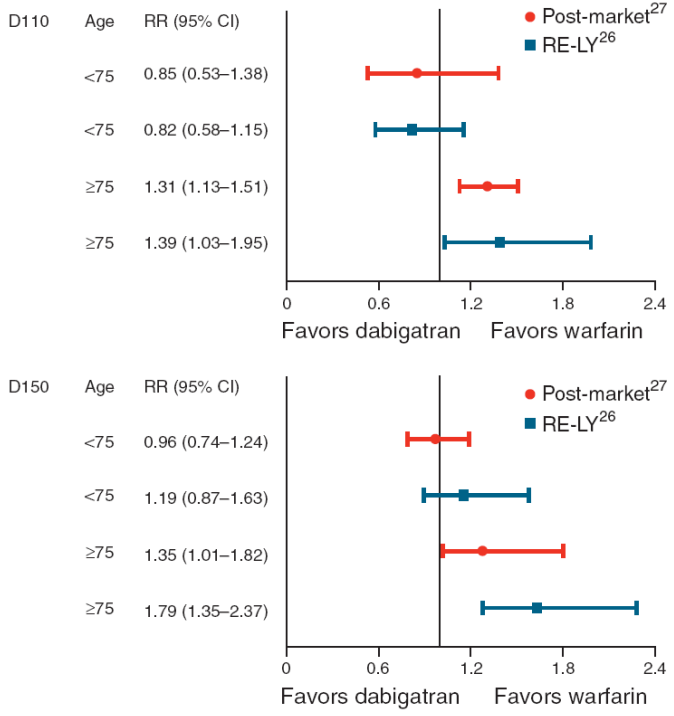
All odds ratios are adjusted for age and sex to take the effect of frequency matching on these factors into account.
— indicates not applicable.

LEVI et al. BLEEDING IN PATIENTS EXCLUDED FROM VKATRIALS. BLOOD, 1 MAY 2008, VOLUME 111, NUMBER 9

GI Bleeding of NOAC - Post-market studies

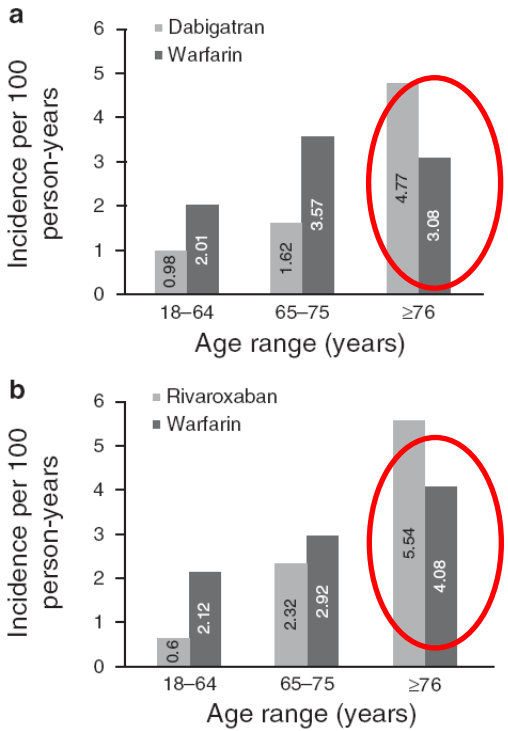
The increased risk of NOAC-associated vs. warfarin associated MGIB identified in the RCTs of dabigatran and rivaroxaban may be most clinically relevant in **patients over 75 years of age.**

	Age Group (n)	Men, Hazard Ratio (95% CI)	Women, Hazard Ratio (95% CI)
Ischemic stroke			
	65–74 (55 761)	0.69 (0.42–1.14)	0.81 (0.51–1.31)
	75–84 (57 345)	0.98 (0.64–1.51)	0.89 (0.64–1.26)
	≥85 (21 308)	0.89 (0.41–1.90)	0.60 (0.40–0.91)
Intracranial hemorrhage			
	65–74 (55 761)	0.32 (0.15–0.68)	0.13 (0.04–0.44)
	75–84 (57 345)	0.27 (0.14–0.50)	0.59 (0.35–0.98)
	≥85 (21 308)	0.51 (0.18–1.48)	0.26 (0.12–0.56)
Major gastrointestinal bleeding			
	65–74 (55 761)	0.83 (0.60–1.14)	0.99 (0.72–1.37)
	75–84 (57 345)	1.02 (0.79–1.31)	1.50 (1.20–1.88)
	≥85 (21 308)	1.55 (1.04–2.32)	2.18 (1.61–2.97)
Mortality			
	65–74 (55 761)	0.81 (0.62–1.05)	0.72 (0.52–0.99)
	75–84 (57 345)	0.73 (0.58–0.92)	0.82 (0.65–1.03)
	≥85 (21 308)	0.92 (0.64–1.33)	1.24 (0.96–1.60)



GI Bleeding of NOAC - Post-market studies

The increased risk of NOAC-associated vs. warfarin associated MGIB identified in the RCTs of dabigatran and rivaroxaban may be most clinically relevant in **patients over 75 years of age.**



Desai et al. GI Bleeding in AF Patients Taking DOACs. Am J Gastroenterol Suppl 2016; 3:13 – 21

GI Bleeding of NOAC - Post-market studies

Table 4. Stratified Analysis in Propensity Score Matched Rivaroxaban vs Dabigatran Users

	Rivaroxaban (n = 15,787)		Dabigatran (n = 15,787)		Rivaroxaban vs dabigatran (n = 31,574)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	222	2.74	215	2.02	1.20 (1.00–1.45)	
Age						.10
18–64 y	26	1.05	14	0.46	2.03* (1.06–3.90)	
65–74 y	66	2.54	54	1.56	1.44* (1.00–2.06)	
≥75 y	130	4.29	147	3.54	1.06 (0.84–1.34)	

Table 5. Stratified Analysis in Propensity Score Matched Apixaban vs Dabigatran Users

	Apixaban (n = 6,542)		Dabigatran (n = 6,542)		Apixaban vs dabigatran (n = 13,084)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27–0.58)	
Age						.54
18–64 y	2	0.34	7	0.73	0.38 (0.08–1.84)	
65–74 y	5	0.69	29	2.12	0.25** (0.10–0.65)	
≥75 y	26	2.43	85	4.06	0.45*** (0.29–0.71)	

Table 6. Stratified Analysis in Propensity Score–Matched Apixaban vs Rivaroxaban Users

	Apixaban (n = 6565)		Rivaroxaban (n = 6565)		Apixaban vs rivaroxaban (n = 13,130)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22–0.49)	
Age						.36
18–64 y	2	0.34	6	0.81	0.38 (0.08–1.89)	
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

GI Bleeding of NOAC
- Lessons from Post-market studies

- The increased risk of DOAC-associated vs. warfarin associated MGIB identified in the RCTs of dabigatran and rivaroxaban may be most clinically relevant in patients over 75 years of age. The effect of age on bleeding risk in patients taking apixaban or edoxaban has not yet been published.

- The morbidity and mortality associated with MGIB is generally less than that associated with ICH, stroke, or systemic embolus. Specific reversal agents such as idarucizumab and andexanet alfa should further improve the outcome of bleeding events. Thus, in general, treatment should be guided by drug efficacy considerations over risk of MGIB.

- Clinical characteristics such as age, concurrent medication use (in particular antiplatelet use), and comorbidities (in particular renal function) predict MGIB.

Desai et al. GI Bleeding in AF Patients Taking DOACs. Am J Gastroenterol Suppl 2016; 3:13 – 21

GI Bleeding of NOAC
- Lessons from Post-market studies

- In a recent Asian study of dabigatran users who had a prior history of peptic ulcer disease or GI bleeding, proton pump inhibitor use was associated with a reduced risk of upper GI bleeding (HR 0.29, 95 % CI 0.15 – 0.54)

- In comparison with MGIB associated with warfarin, antiplatelet agents, or NSAIDs, bleeding associated with dabigatran (and perhaps the other NOAC agents) occurs more from a source in the lower vs. the upper GI tract. The prevalence of site-unspecified MGIB in numerous studies suggests that the small bowel may be a source of bleeding in this context.

- Initiation of NOAC treatment may unmask occult luminal GI tract cancers by inducing GI bleeding. Appropriate screening of patients before anticoagulant initiation should be considered, and bleeding after drug initiation generally warrants investigation.

Desai et al. GI Bleeding in AF Patients Taking DOACs. Am J Gastroenterol Suppl 2016; 3:13 – 21

GI Bleeding of NOAC - Prevention strategies

1. Confirm that NOAC indication is appropriate and that there are no absolute contra-indications to NOAC administration.
2. Confirm that NOAC dosage is appropriate (e.g. dose dabigatran as indicated by creatinine clearance).
3. Screen all patients for presence of on-going GI bleeding by history (history of recent melena or rectal bleeding) and physical exam (digital rectal exam). Consider screening with laboratory testing (faecal occult blood testing, haemoglobin evaluation and evaluation of iron stores). If GI bleeding is suggested, consider GI investigation prior to initiating NOAC treatment.
4. Assess for history of previous GI bleeding and consider diagnostic interventions (e.g. endoscopy) or therapeutic interventions (e.g. concomitant administration of a PPI) where indicated.
5. Assess for co-administration of drugs such as anti-platelet agents or NSAIDs which increase the risk of NOAC related GI bleeding.
6. If patient is concurrently taking anti-platelet medication, weigh the risks, benefits, and alternatives of continuing NOAC plus anti-platelet agent.
7. If patient is taking chronic NSAIDs, consider alternative therapies and/or co-administration of a gastroprotective agent such as a PPI.
8. Consider non-medication risk factors such as alcohol intake, and encourage risk factor modification.
9. Assess creatinine clearance and institute renal protective measures as indicated (especially in patients receiving dabigatran).
10. Counsel the patient regarding the potential for increased risk of GI bleeding in the setting of dehydration, concomitant illness, or concomitant medication use, and the recommended measures in these settings (e.g. seeking prompt medical attention, maintaining hydration, performing laboratory assessments of renal function).

Desai et al. New oral anticoagulants and GI bleeding. Thromb Haemost 2013; 110: 205–212