8th Annual Emirates Cardiac Society Conference

ACC Middle East Conference 2017

DUBAI

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Individual Therapeutic Selection Of Anti-coagulants And Peri-procedural Management

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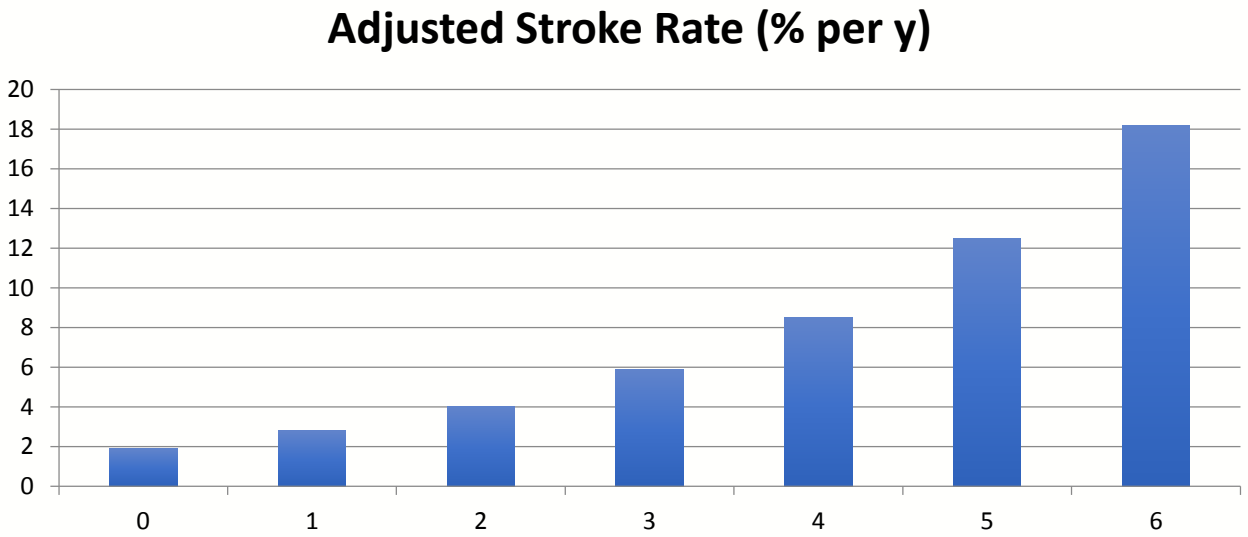
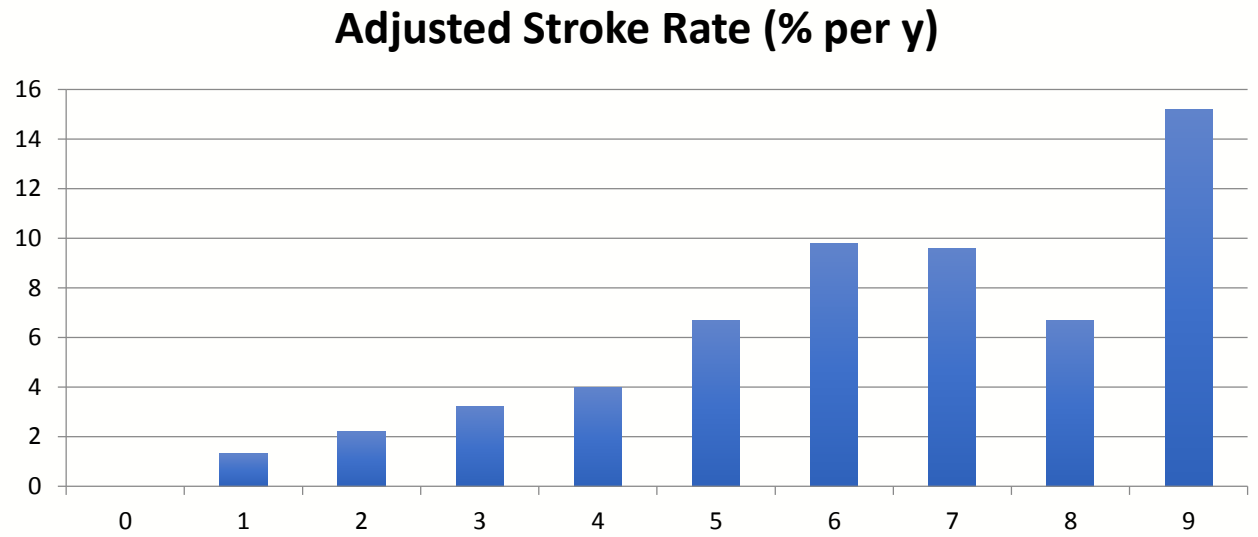
ACC Middle East Conference 2017

Outline

- Does the patient need anticoagulation?
- Review of clinical evidence for each anticoagulant
- Particular circumstances:
  - Prior GI bleed
  - Prior CNS bleed
  - CAD with or without stent
- Periprocedural management

Risk of Stroke in Atrial Fibrillation
$CHADS_2$-CHA_2DS_2-VASc Scores





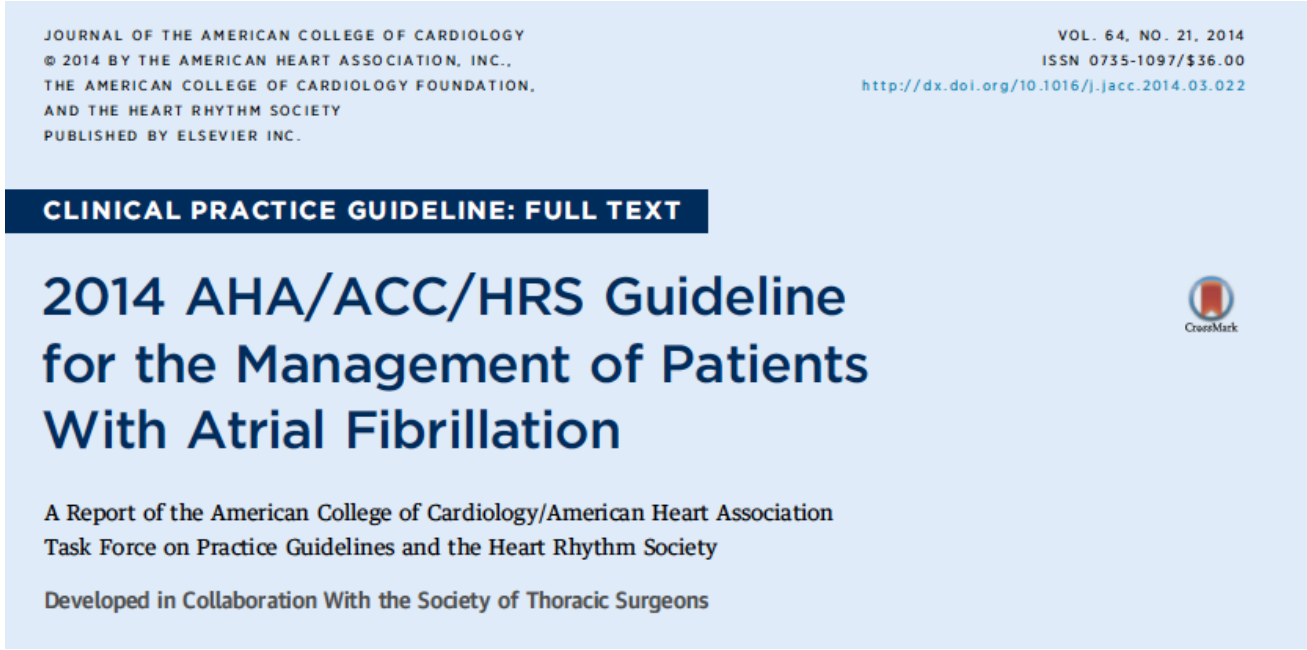
$CHADS_2$	
Congestive HF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6

CHA_2DS_2-VASc	
Congestive HF	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 y	1
Sex category (i.e., female sex)	1
Maximum score	9

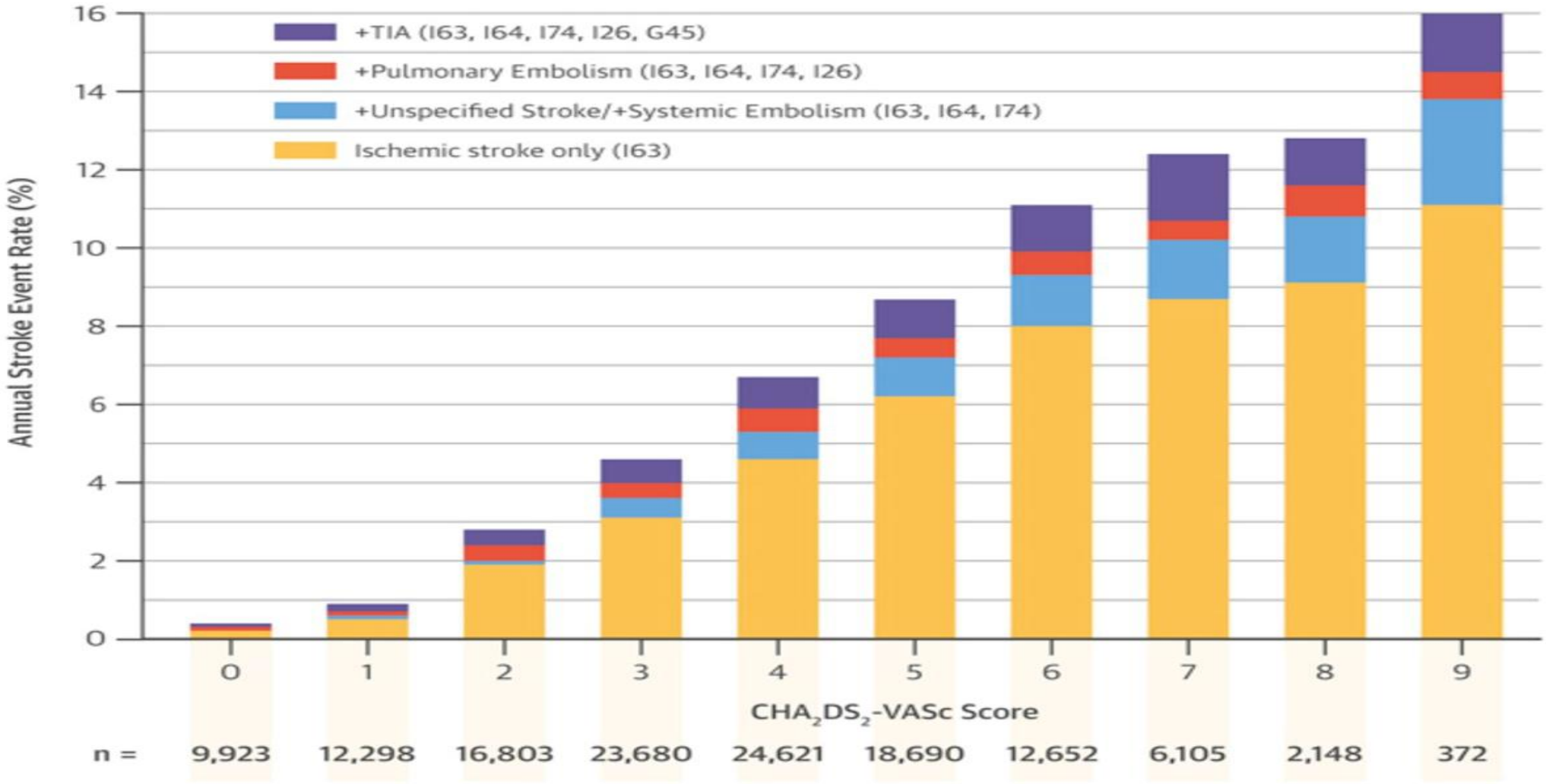
J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021

When to anticoagulate patients with AF

- Benefits of stroke risk reduction must outweigh risks of bleeding.
- CHADS2>1
- CHADS-VASc ≥1 for men and ≥2 for women



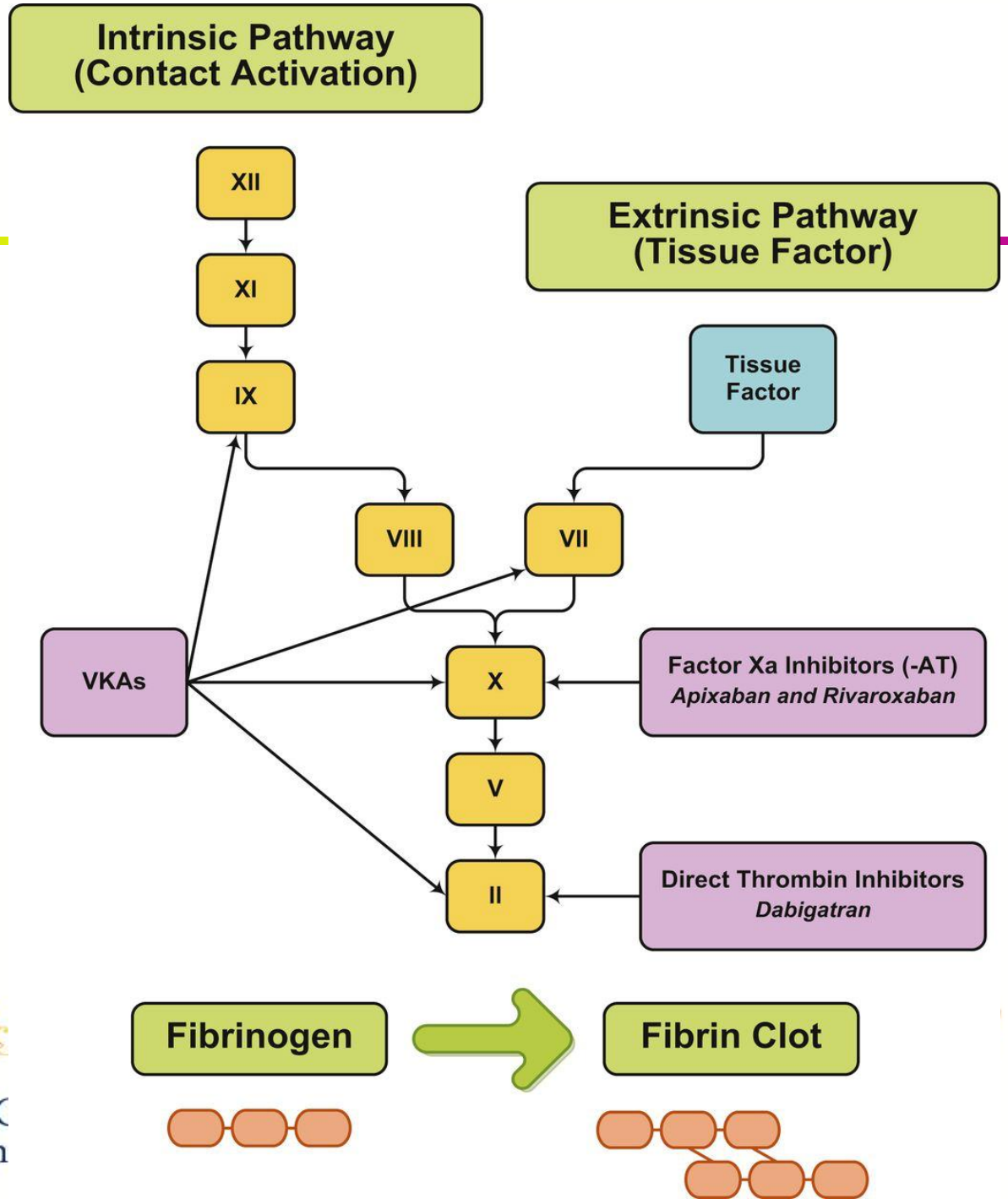
Validation of CHADS-VASc



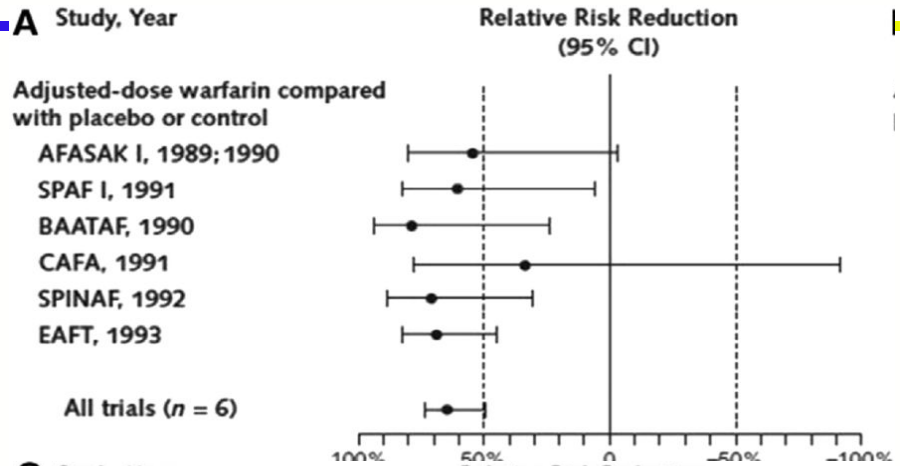
Friberg, L. et al. J Am Coll Cardiol. 2015; 65(3):225-32.

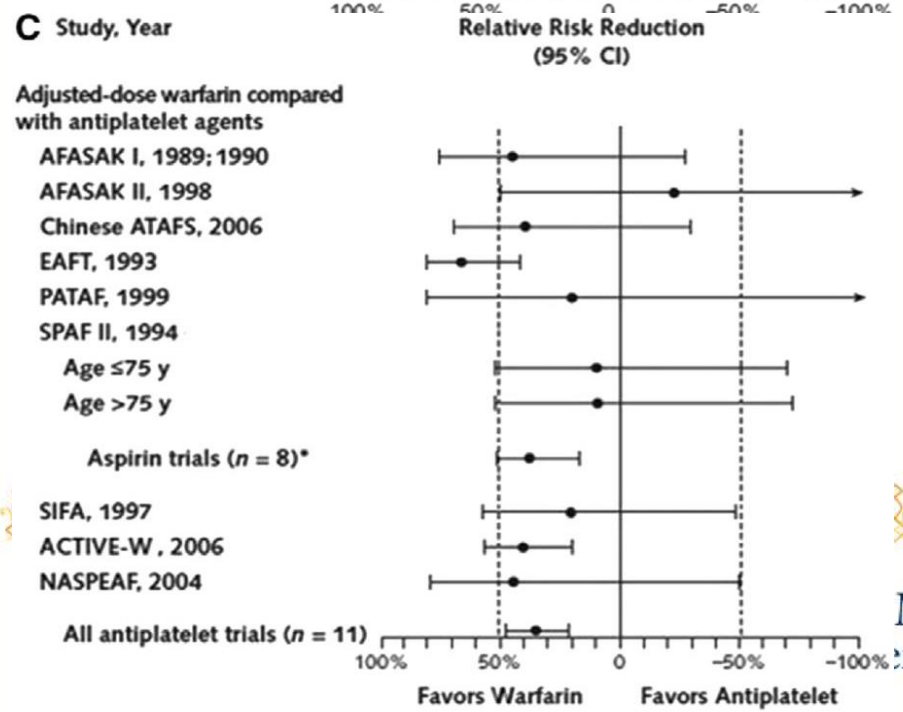
Oral anticoagulants

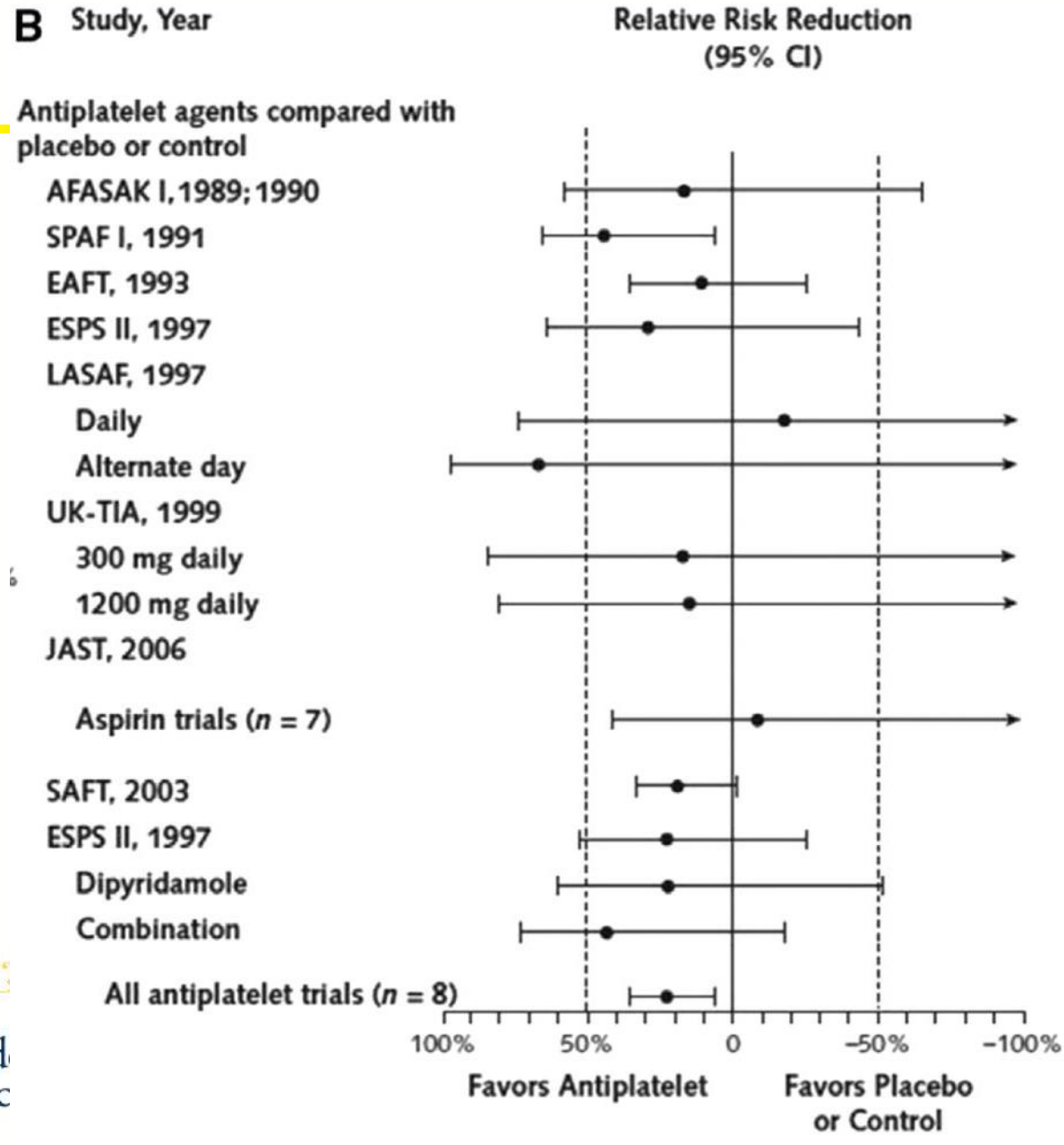
- Warfarin
- Direct oral anticoagulants
  - Direct thrombin inhibitor: dabigatran
  - Factor X antagonists: apixaban, rivaroxaban, edoxaban



Which anticoagulant to use? Warfarin vs anti-platelet

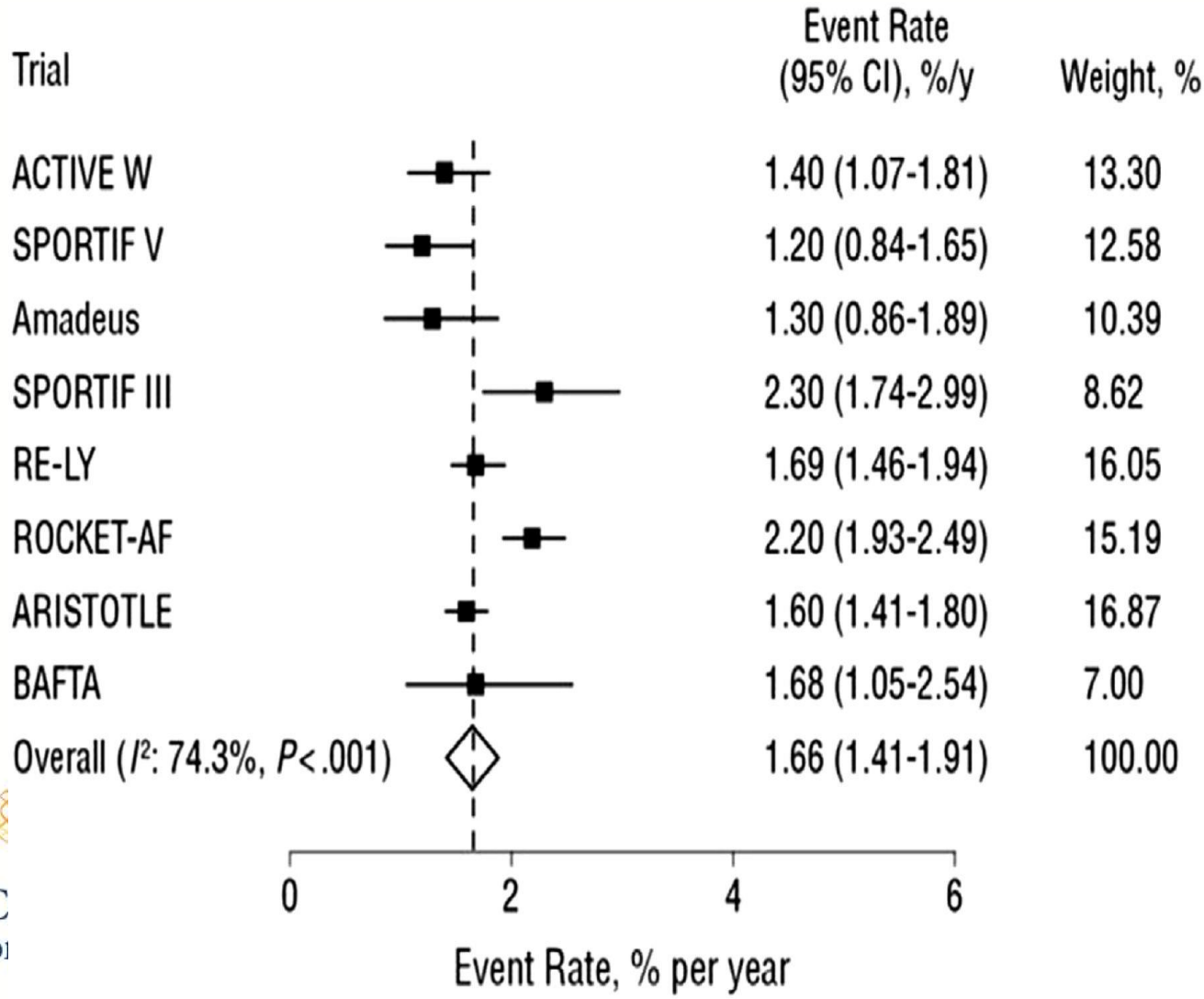






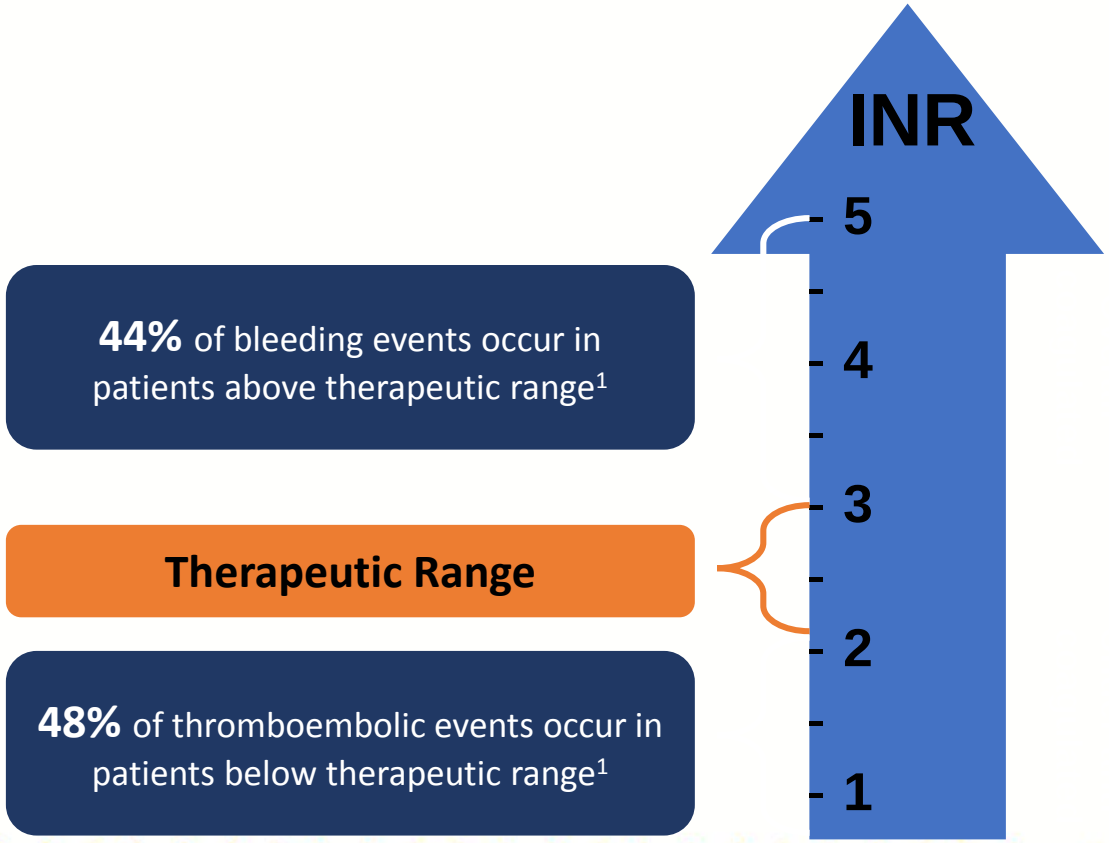
Warfarin pooled data

- Inexpensive and effective for prevention of stroke and systemic embolization in patients with nonvalvular AF
- Requires frequent blood testing to maintain dosing within a narrow therapeutic window
  - Affected by drug and dietary interactions
  - Bleeding is a complication
  - Must be stopped prior to planned surgery
- Overall stroke risk 1.66%/year



Warfarin

- Warfarin is an effective means of stroke reduction in patients with AF, but can present challenges
  - Many patients spend a significant amount of time outside of the therapeutic range
  - Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans[2]

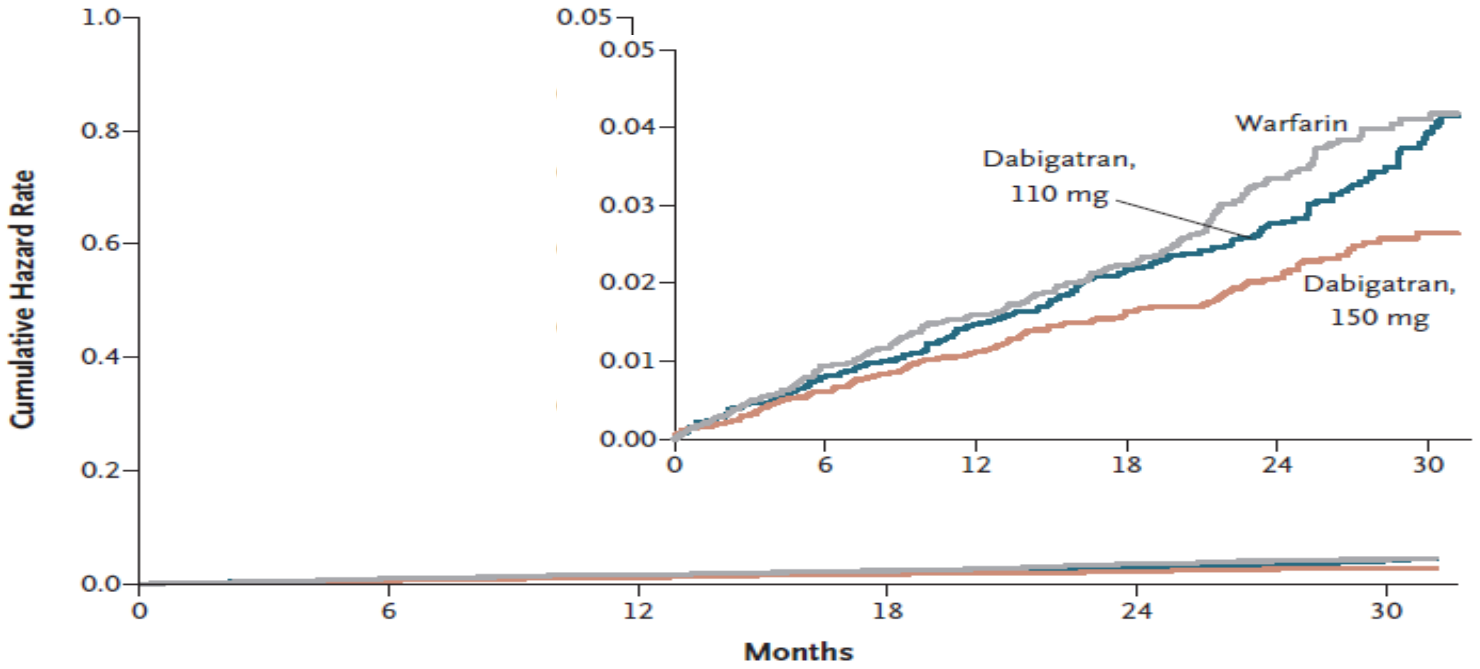


Novel Oral Anticoagulants (NOACs)

	Dadigatran[1]	Rivaroxaban[2]	Apixaban[3]	Edoxaban[4]
Comparator	Warfarin	Warfarin	Warfarin	Warfarin
Total enrolled subjects	18,113	14,264	18,201	21,105
Trial design	Randomized, controlled, non-inferiority (doses of dabigatran were blinded)	Randomized, controlled, double-blind, non-inferiority	Randomized, controlled, double-blind, non-inferiority	Randomized, double-blind, double-dummy
Median duration of follow-up	2 years	1.94 years	1.8 years	2.8 years
Average $CHADS_2$ score	2.1	3.5	2.1	2.8
Results (primary outcome = stroke or systemic embolism)	Reduction in primary outcome compared with warfarin	Reduction in primary outcome compared with warfarin	Reduction in primary outcome compared with warfarin	Noninferior to warfarin

Atrial Fibrillation and Dabigatran

Connolly S et al *N Engl J Med 2009*; 361:1139-1151



No. at Risk

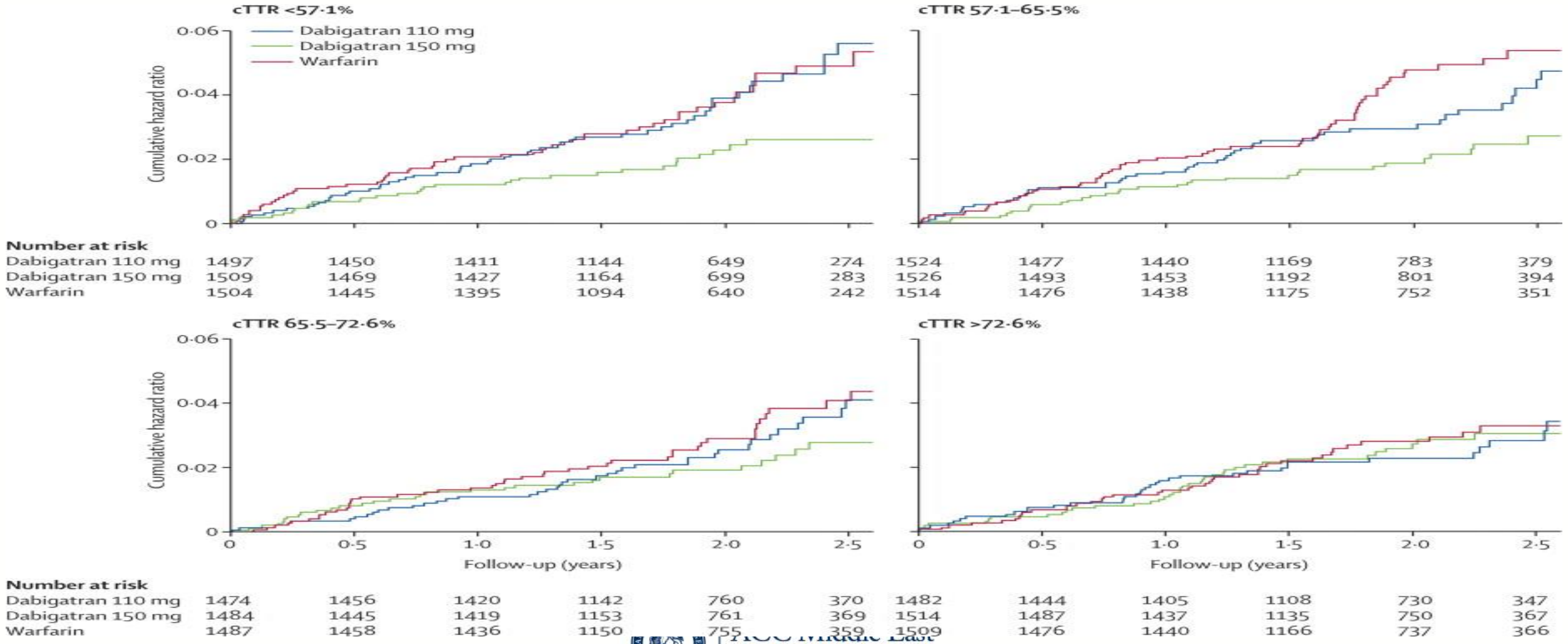
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Stroke and Dabigatran

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03

Atrial Fibrillation and Stroke:
Dabigatran vs Therapeutic Warfarin



Wallentin et al *Lancet.* 2010;376(9745):975-83.

Dabigatran and bleeding

Connolly S et al *N Engl J Med 2009*; 361:1139-1151

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	
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
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

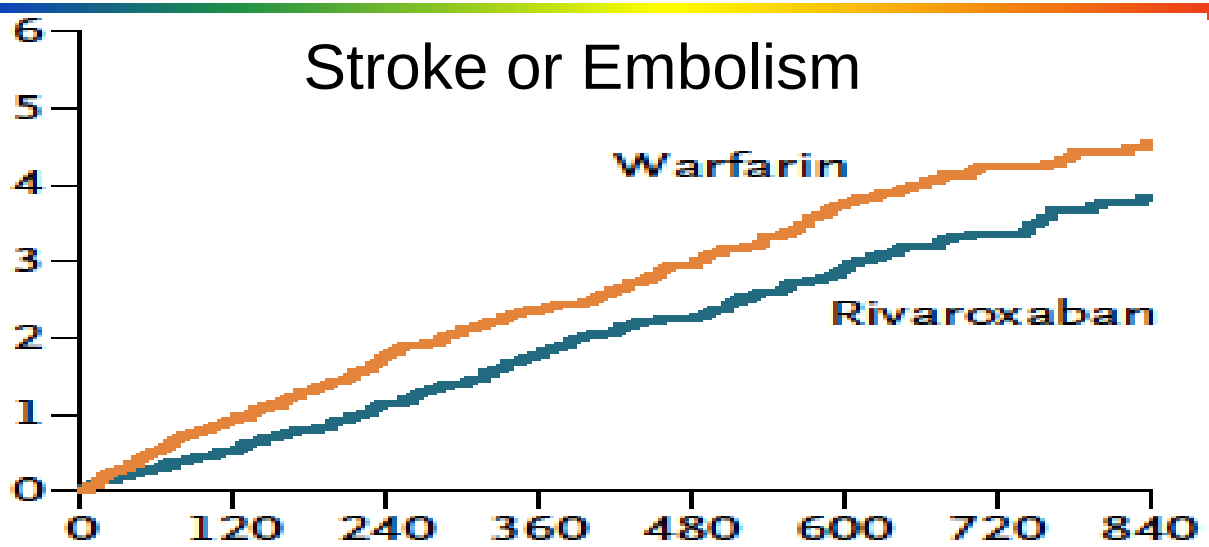
* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.

† Gastrointestinal bleeding could be life threatening or non–life threatening.

‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Atrial Fibrillation and Rivaroxaban

Patel et al *N Engl J Med* 2011; 365:883-891



	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	Total	Event Rate (100 Pt-Yr)‡	Total	Event Rate (100 Pt-Yr)‡	Hazard Ratio (95% CI)§	P Value‖
Secondary efficacy endpoints, no. (%)¶						
Stroke, non-CNS embolism, and vascular death	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74,0.99)	0.034
Stroke, non-CNS embolism, vascular death, and myocardial infarction	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74,0.96)	0.010
Stroke	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70, 1.03)	0.092
Hemorrhagic	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37, 0.93)	0.024
Ischemic	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75, 1.17)	0.581

Bleeding and Rivaroxaban

Patel et al *N Engl J Med* 2011; 365:883-891

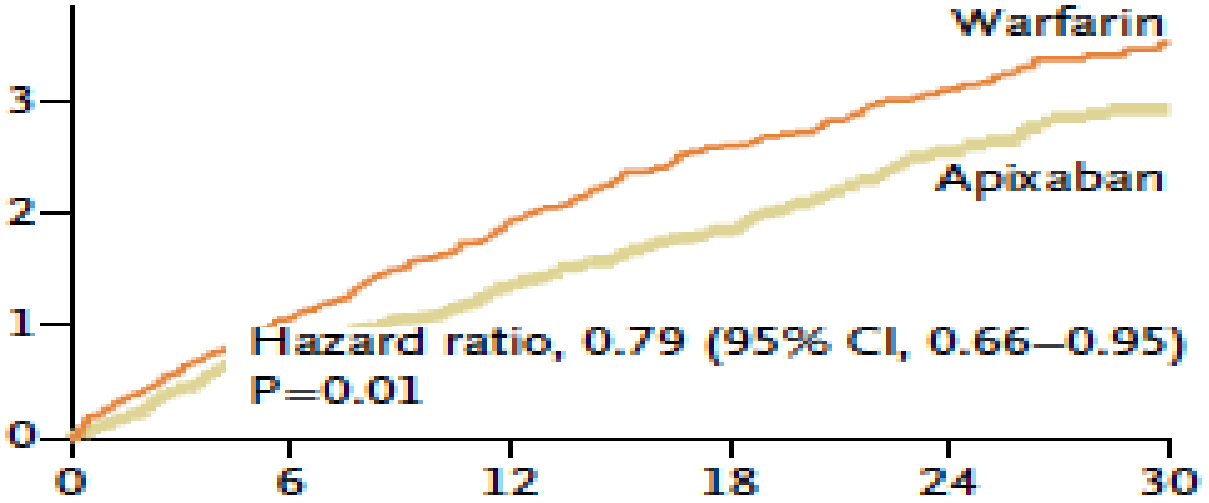
Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

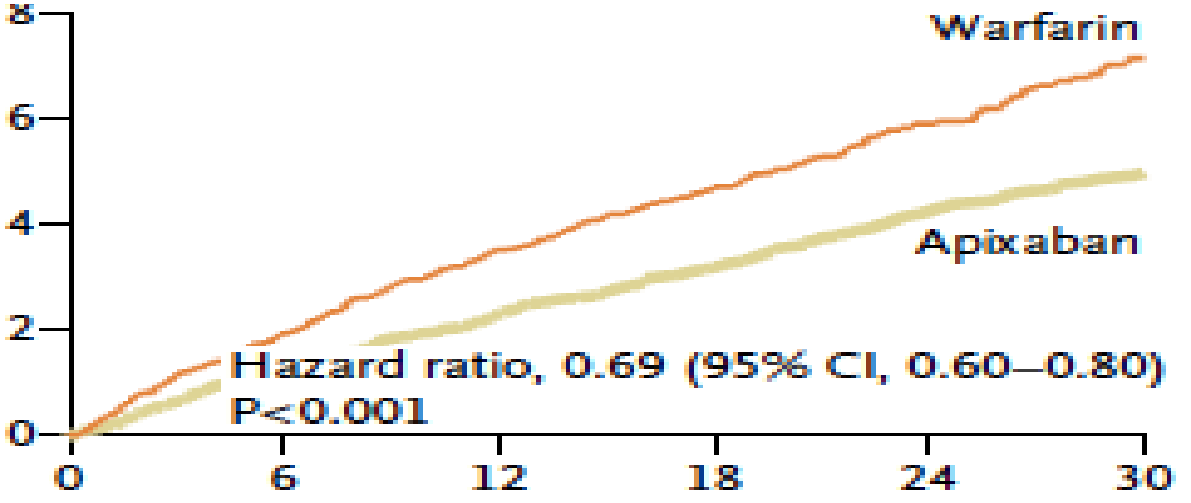
Atrial Fibrillation and Apixaban

Granger et al *N Engl J Med* 2011; 365:981-992

Stroke or Embolism



Bleeding



Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047

Bleeding and Apixaban

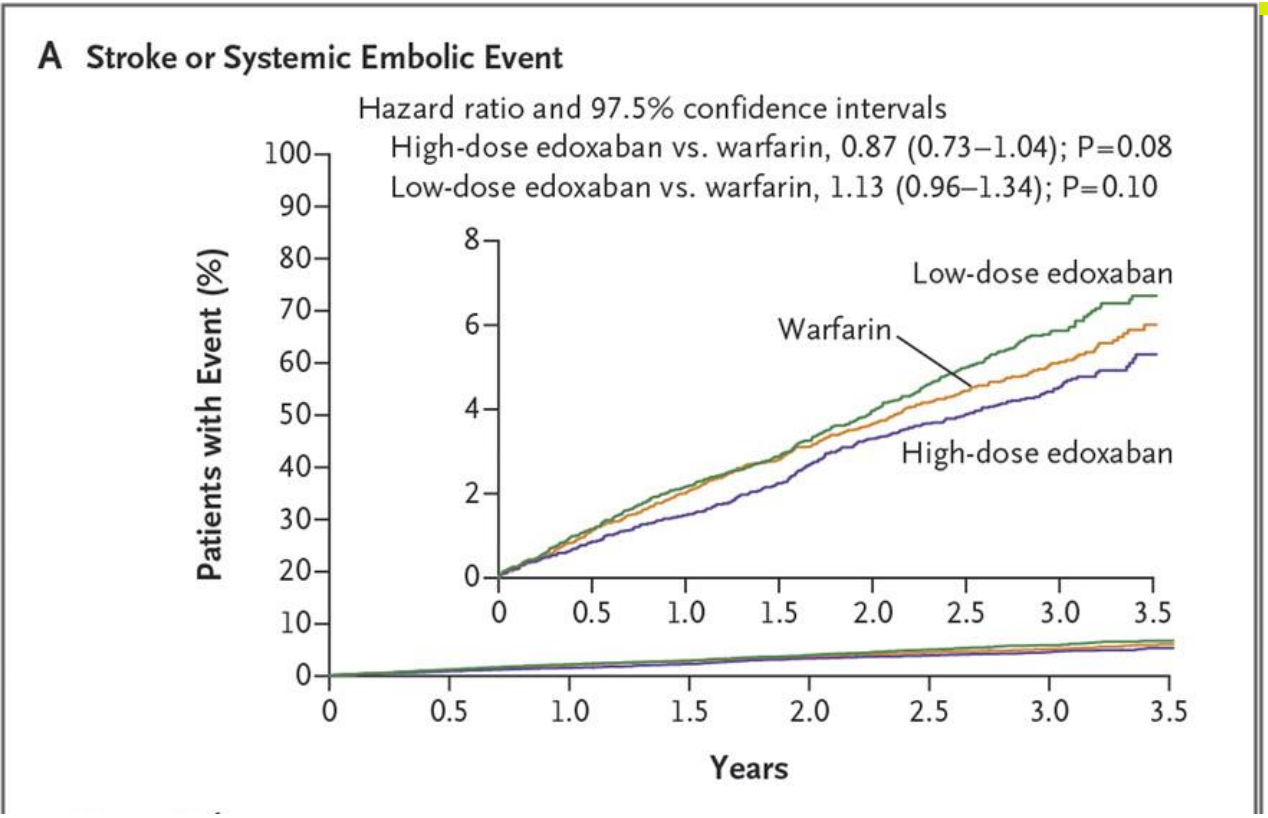
Granger et al *N Engl J Med* 2011; 365:981-992

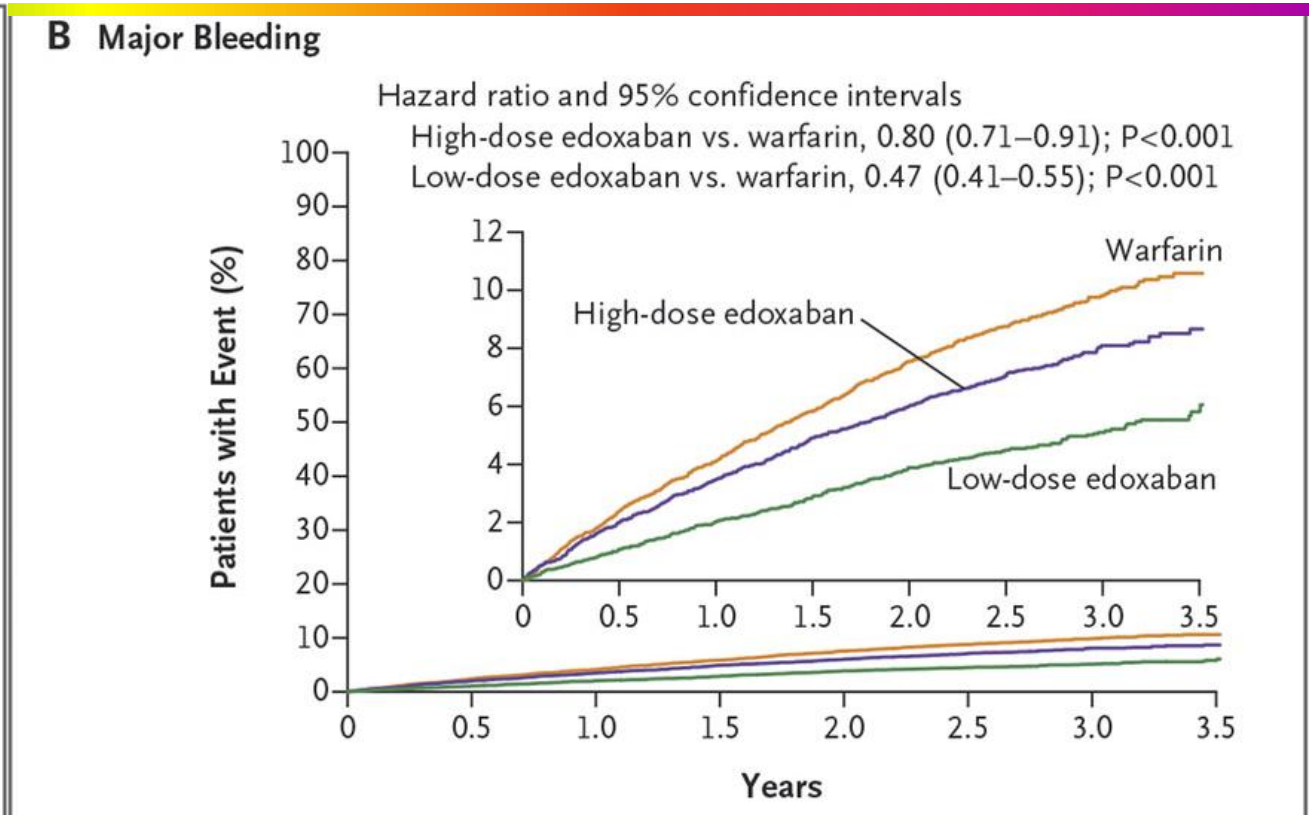
Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

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

Atrial Fibrillation and Edoxaban

Giuliano et al N Engl J Med 2013; 369:2093-2104





End Point	Warfarin (N=7036)		High-Dose Edoxaban (N=7035)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7034)		Low-Dose Edoxaban vs. Warfarin	
					Hazard Ratio (95% CI)	P Value			Hazard Ratio (95% CI)	P Value
Stroke	317	1.69	281	1.49	0.88 (0.75–1.03)	0.11	360	1.91	1.13 (0.97–1.31)	0.12
Hemorrhagic	90	0.47	49	0.26	0.54 (0.38–0.77)	<0.001	30	0.16	0.33 (0.22–0.50)	<0.001
Ischemic	235	1.25	236	1.25	1.00 (0.83–1.19)	0.97	333	1.77	1.41 (1.19–1.67)	<0.001

Bleeding and Edoxaban

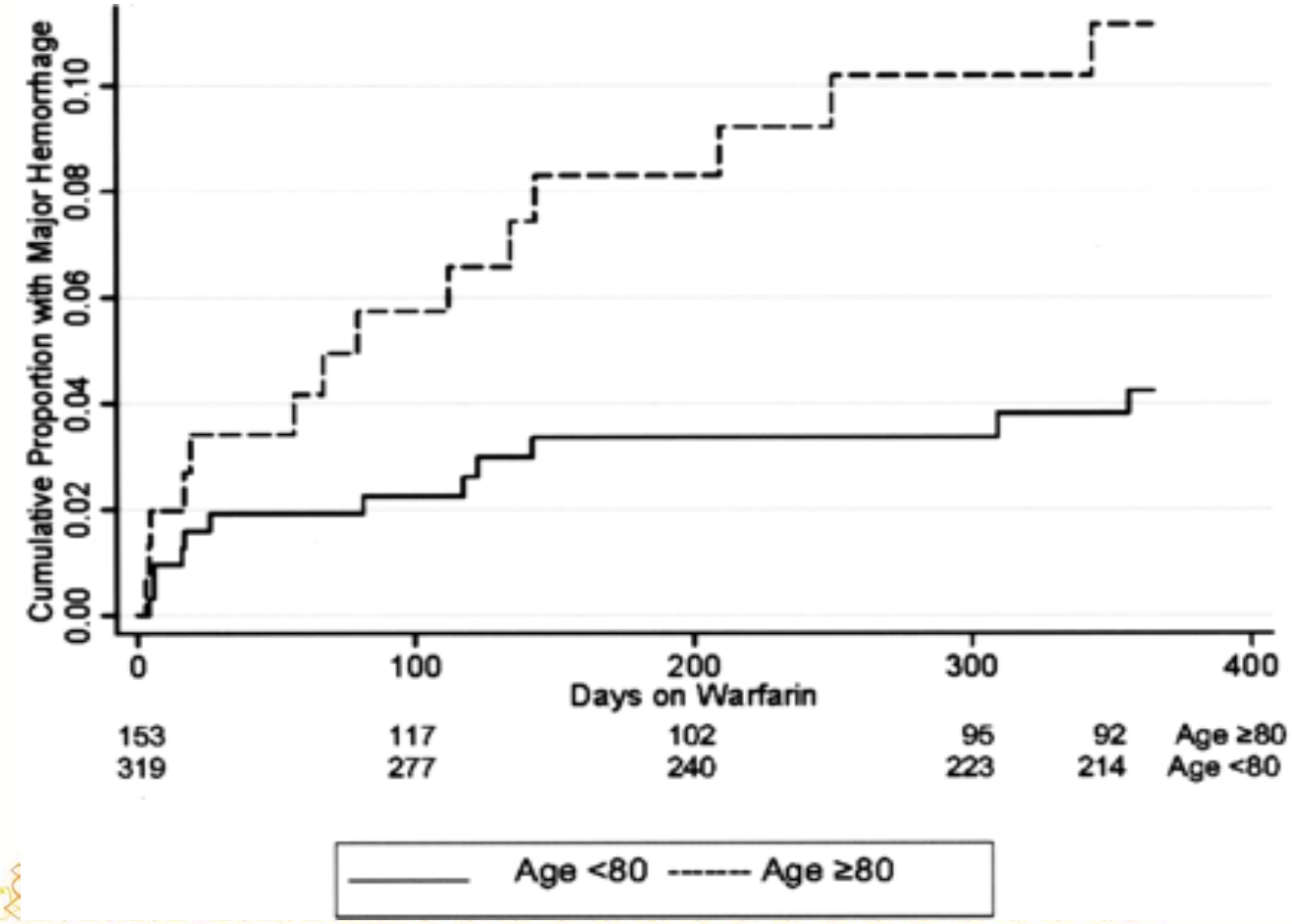
Giuliano et al N Engl J Med 2013; 369:2093-2104

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	
	no. of patients with event	*% of patients/yr*	*no. of patients with event*	*% of patients/yr*	Hazard Ratio (95% CI)	P Value	*no. of patients with event*	*% of patients/yr*	Hazard Ratio (95% CI)	P Value
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	—	—	—
Life-threatening bleeding	122	0.78	62	0.40	0.51 (0.38–0.70)	<0.001	40	0.25	0.32 (0.23–0.46)	<0.001
Clinically relevant nonmajor bleeding	1396	10.15	1214	8.67	0.86 (0.79–0.93)	<0.001	969	6.60	0.66 (0.60–0.71)	<0.001

Oral anticoagulation and bleeding Warfarin

- Real-life annual risk of bleeding 6-8% rather than 1-3% of clinical trials[1]
  - Annual risk of 13% in those older than 80 y



1. Circulation. May 29 2007;115(21):2689-2696

Oral anticoagulation and bleeding
Dabigatran

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

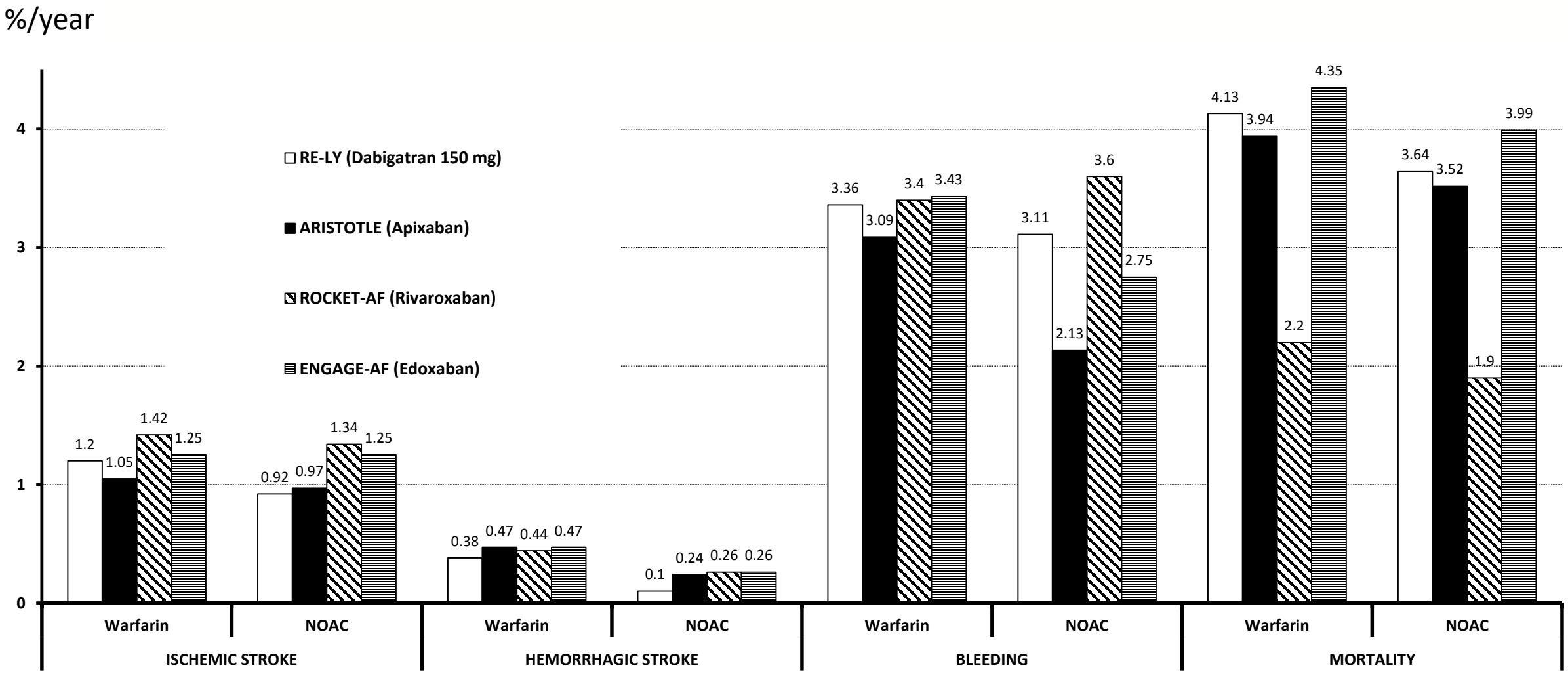
Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Southworth et al N Engl J Med 2013; 368:1272-1274

NOACs Compared with Warfarin: Clinical Trial Summary

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF
Drug	**Dabigatran 150 mg/d**	**Rivoraxaban 20 mg/day**	**Apixaban 5 mg bid**	**Edoxaban 60 mg/day**
$CHADS_2$ score	2.2	3.5	2.1	2.8
TTR, control	67%	58%	66%	68%
Ischemic stroke	0.76 (0.60-0.98)	0.94 (0.75-1.17)	0.92 (0.74-1.14)	1.00 (0.83-1.19)
Hemorrhagic stroke	0.26 (0.14-0.49)	0.59 (0.37-0.93)	0.51 (0.34-0.75)	0.54 (0.38-0.77)
All-cause mortality	0.88 (0.77-1.00)	0.85 (0.70-1.02)	0.89 (0.80-0.998)	0.92 (0.83-1.01)
Major bleed	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.80 (0.71-0.91)
GI bleeding	1.50 (1.19-1.89)	1.39 (1.19-1.61)	0.89 (0.70-1.15)	1.23 (1.02-1.50)

Warfarin vs NOACs



Price, Valderrábano. *Circulation* 2014;130:202-12

Drug Discontinuation/Major Bleeding

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/y)
Rivaroxaban[1]	24%	3.6%
Apixaban[2]	25%	2.1%
Dabigatran[3] (150 mg)	21%	3.3%
Edoxaban[4] (60 mg / 30 mg)	33% / 34%	2.8% / 1.6%
Warfarin [1-4]	17 - 28%	3.1% - 3.6%

There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs

Particular circumstances

- Prior GI bleed:
  - All NOAC show some decrease GI bleed compared with warfarin EXCEPT dabigatran, which increased it.
- Prior CNS bleed:
  - Greater decrease in CNS bleed by dabigatran and apixaban

Particular circumstances: CAD
COMPASS trial N Engl J Med 2017; 377:1319-1330

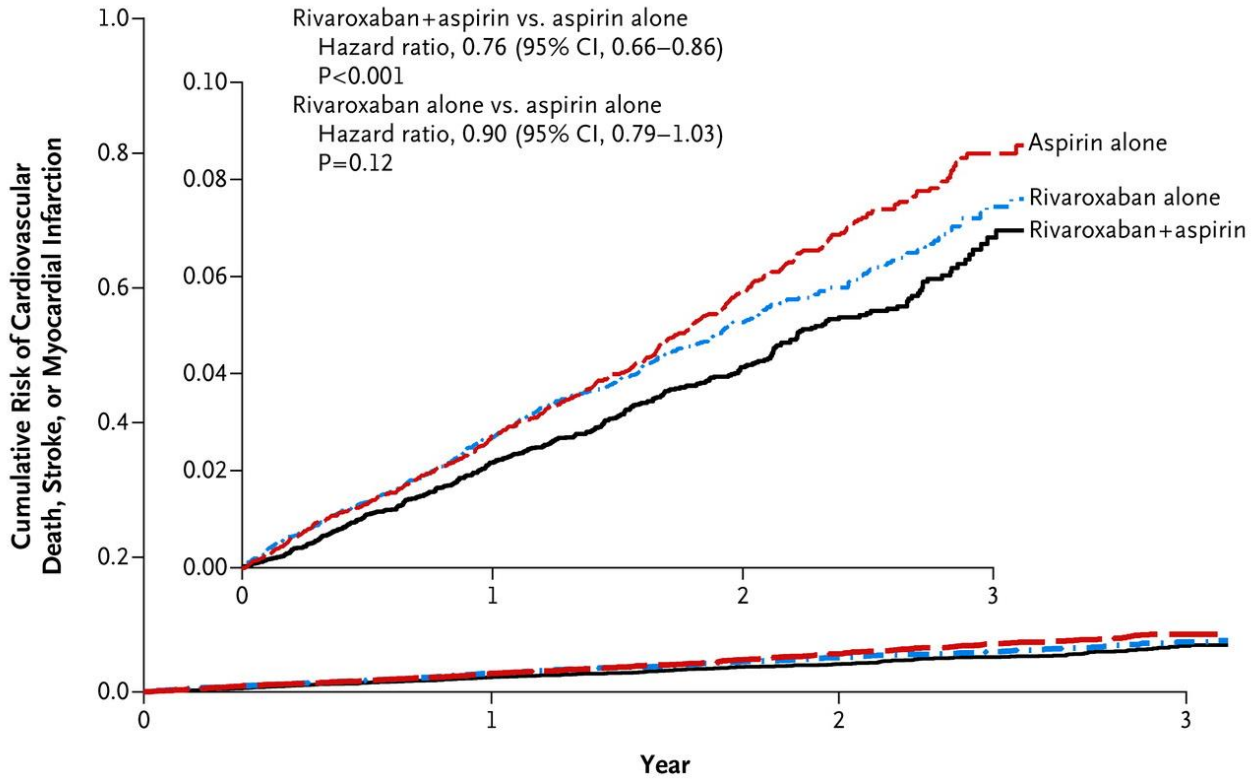


Table 3. Bleeding Events and Net Clinical Benefit.*

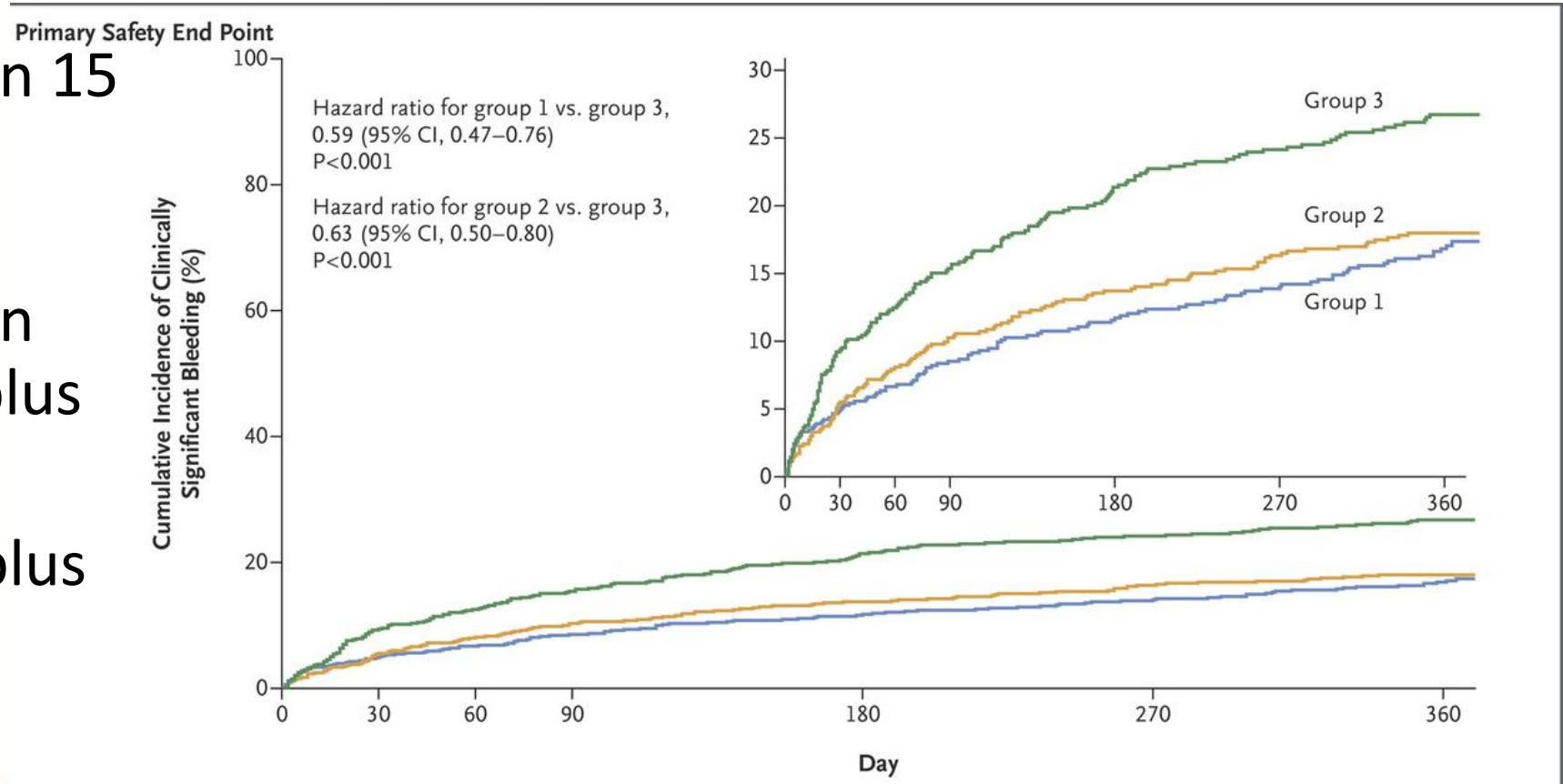
Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001	1.47 (1.16–1.87)	0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40	1.59 (1.00–2.53)	0.05
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09	1.58 (1.13–2.19)	0.006
Major bleeding according to ISTH criteria	206 (2.3)	175 (1.9)	116 (1.3)	1.78 (1.41–2.23)	<0.001	1.52 (1.20–1.92)	<0.001
Transfusion within 48 hr after bleeding	87 (1.0)	66 (0.7)	44 (0.5)	1.97 (1.37–2.83)	<0.001	1.50 (1.03–2.20)	0.03
Minor bleeding	838 (9.2)	741 (8.1)	503 (5.5)	1.70 (1.52–1.90)	<0.001	1.50 (1.34–1.68)	<0.001
Site of major bleeding							
Gastrointestinal	140 (1.5)	91 (1.0)	65 (0.7)	2.15 (1.60–2.89)	<0.001	1.40 (1.02–1.93)	0.04
Intracranial	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
Skin or injection site	28 (0.3)	28 (0.3)	12 (0.1)	2.31 (1.18–4.54)	0.01	2.34 (1.19–4.60)	0.01
Urinary	13 (0.1)	30 (0.3)	21 (0.2)	0.61 (0.31–1.23)	0.16	1.43 (0.82–2.50)	0.20
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001	0.94 (0.84–1.07)	0.36

* ICH denotes intracranial hemorrhage, and ISTH International Society on Thrombosis and Haemostasis.
† If a participant had more than one event of major bleeding, only the most serious bleeding event was counted in these analyses.

Particular circumstances: AF and PCI-Stent PIONEER trial

N Engl J Med 2016; 375:2423-2434

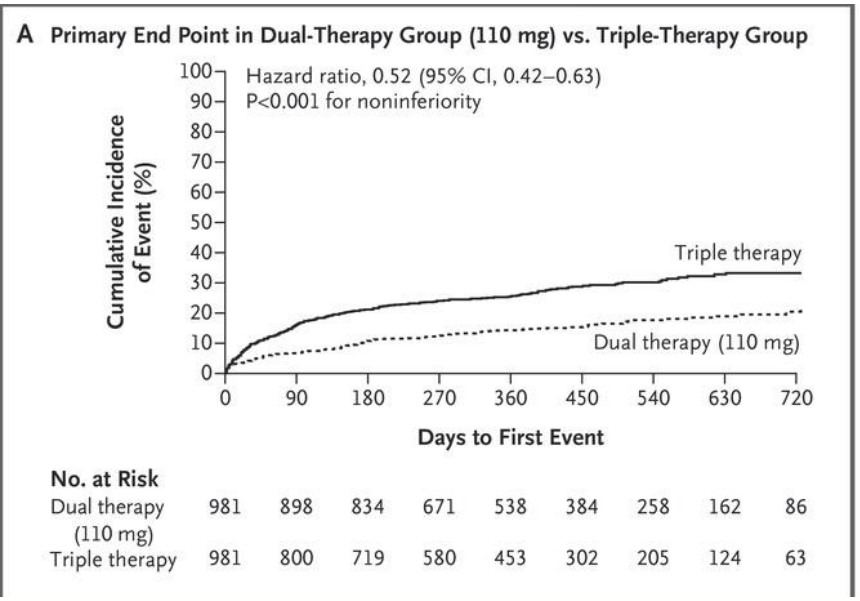
- Group 1: rivaroxaban 15 mg once a day + clopidogrel
- Group 2: rivaroxaban 2.5 mg twice daily plus background DAPT
- Group 3: warfarin plus background DAPT

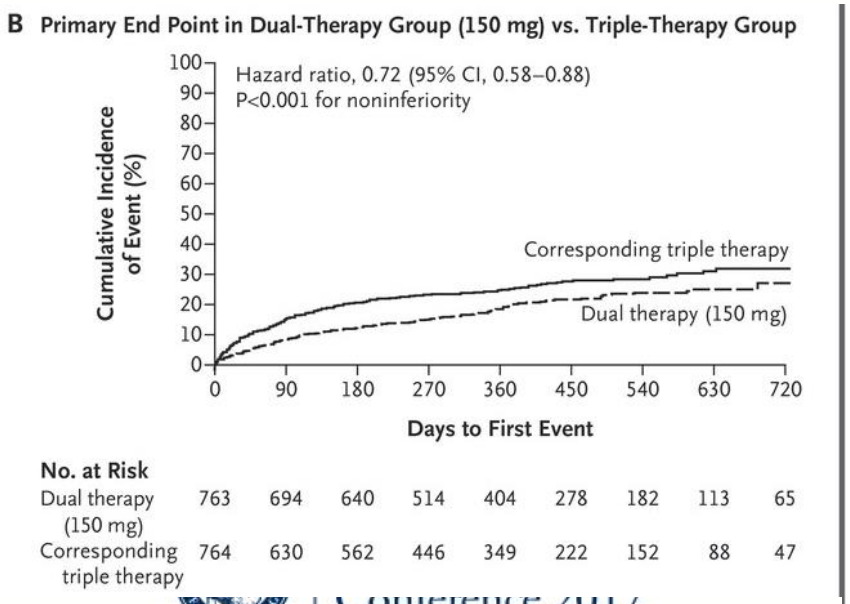


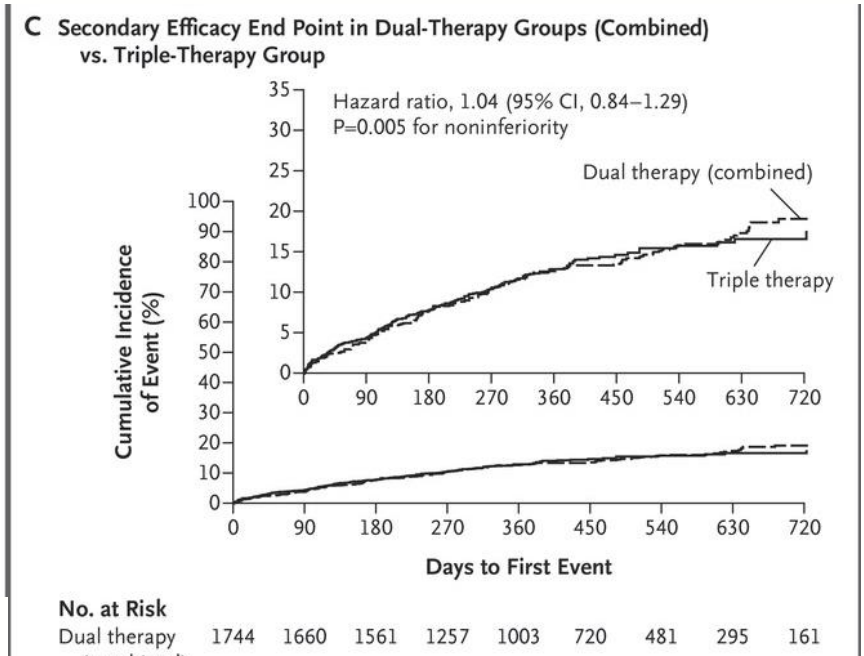
Particular circumstances: AF and PCI-Stent RE-DUAL PCI

N Engl J Med 2017; 377:1513-1524

- Primary end point: major or clinically relevant nonmajor bleeding event during follow-up
- Secondary: composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization







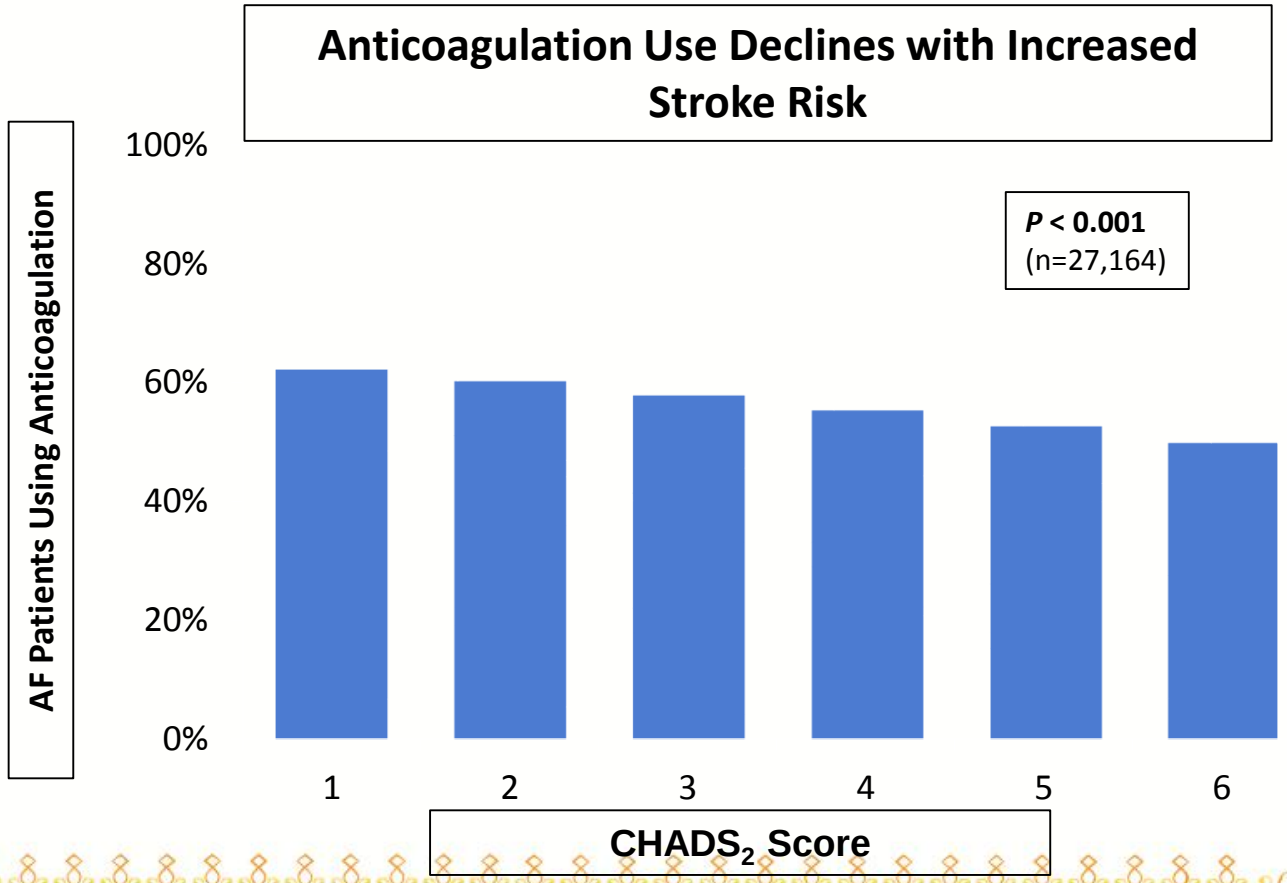
Although OACs May Be Indicated, They Are Under-utilized

Warfarin

- Bleeding risk
- High non-adherence rates
- Regular INR monitoring
- Food and drug interaction issues
- Complicates surgical procedures

NOACs

- Bleeding risk
- High non-adherence rates
- Complicates surgical procedures
- Lack of reversal agents
- High cost



Piccini JP et al. *Heart Rhythm*. 2012;9:1403-1408.

Periprocedural anticoagulation *ACC expert consensus*

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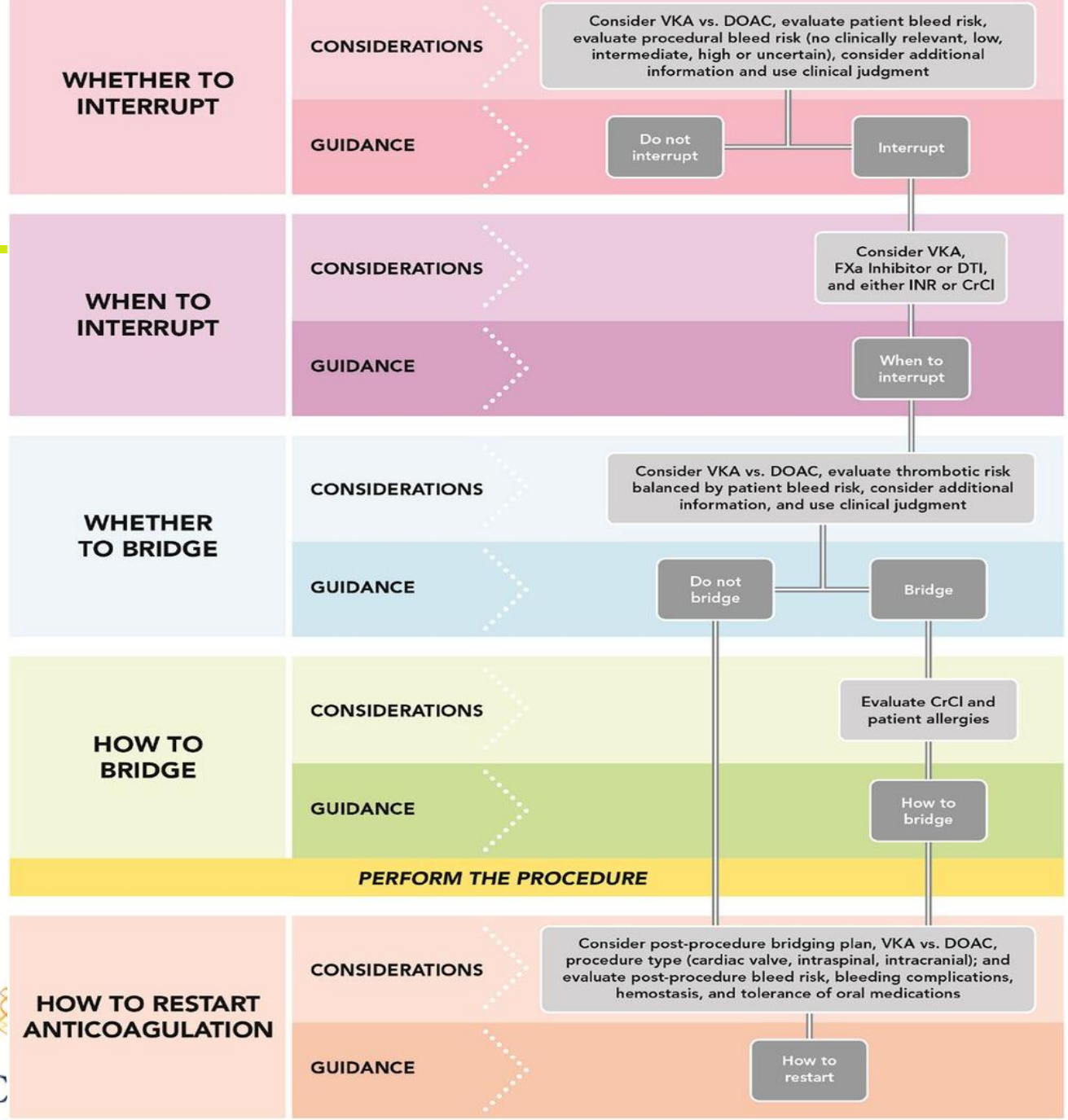
J Am Coll Cardiol. 2017 Feb 21;69(7):871-898.



Estimating procedural risk

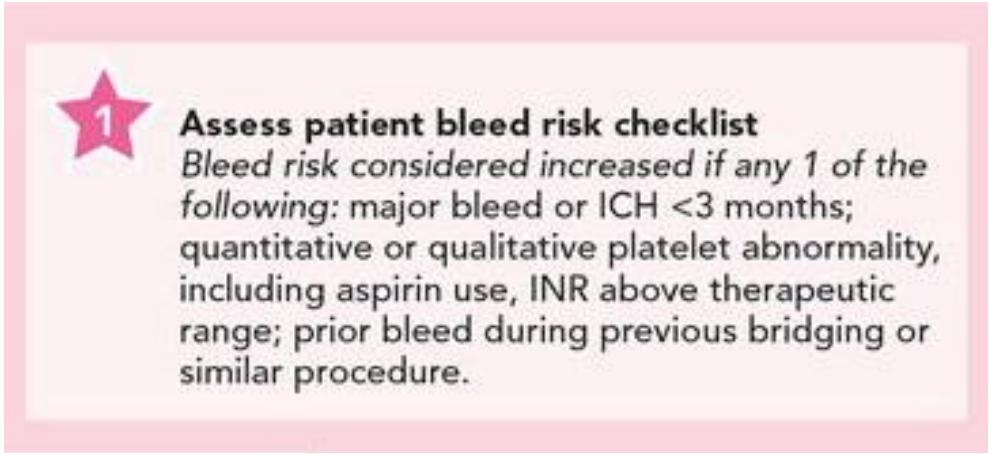
- Extremely variable among different procedures.
- Professional societies have developed a list of procedures and respective risks
- Available as an appendix at

J Am Coll Cardiol. 2017 Feb 21;69(7):871-898.

Procedure Name	Bleed Risk Level			
	Low	Intermediate	High	Uncertain
Lead extraction, mechanical/laser assisted	☐	☐	☒	☐
Ablation, epicardial VT (ventricular tachycardia)	☐	☐	☒	☐
LAAO (left atrial appendage occlusion) (e.g., Watchman device or Lariat procedure)	☐	☐	☒	☐
Ablation, structural VT (ventricular tachycardia)*	☒	☒	☐	☐
Ablation, PVC (premature ventricular complex)*	☒	☒	☐	☐
Ablation, atrial fibrillation*	☒	☒	☐	☐
Ablation, atrial flutter	☒	☐	☐	☐
Implant or generator replacement, CIED (cardiac implantable electronic device)	☒	☐	☐	☐
Implant, subcutaneous ICD (implantable cardioverter defibrillator)	☒	☐	☐	☐
Ablation, SVT (supraventricular tachycardia)	☒	☐	☐	☐
Implant, ILR (implantable loop recorder)	☒	☐	☐	☐
Ablation, endocardial VT (ventricular tachycardia)	☒	☐	☐	☐
Most AF ablation	☒	☐	☐	☐

Estimating patient risk

- HAS-BLED and others bleeding risks estimates are nonspecific for procedures
- *Expert consensus:*

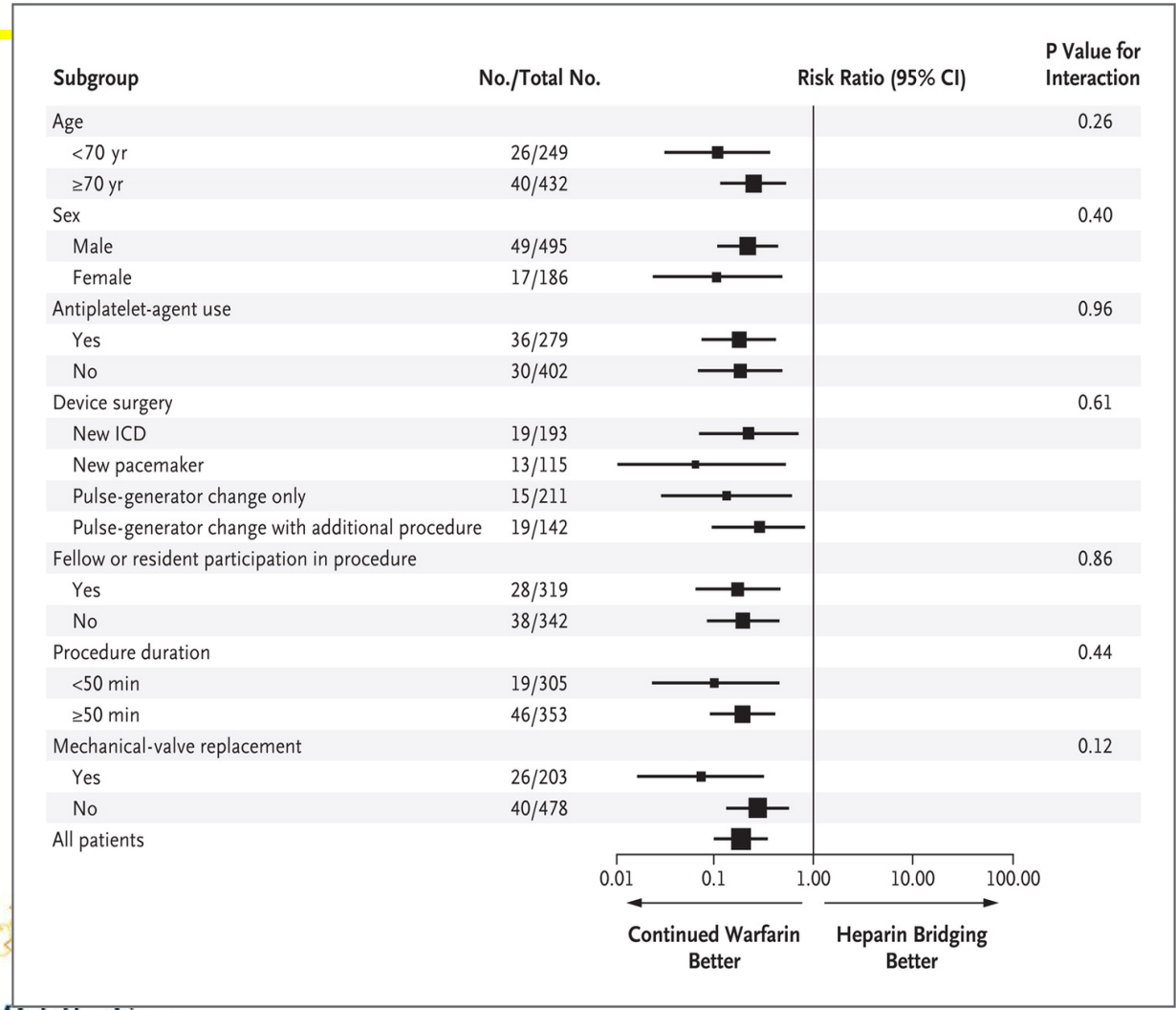


J Am Coll Cardiol. 2017 Feb 21;69(7):871-898.

Periprocedural anticoagulation peri-device implant

Table 3. Primary and Secondary Outcomes.*

Outcome	Heparin Bridging (N=338)	Continued Warfarin (N=343)	Relative Risk (95% CI)	P Value
Primary outcome				
Clinically significant hematoma — no. (%)	54 (16.0)	12 (3.5)	0.19 (0.10–0.36)	<0.001
Components of primary outcome				
Hematoma prolonging hospitalization — no. (%)	16 (4.7)	4 (1.2)	0.24 (0.08–0.72)	0.006
Hematoma requiring interruption of anticoagulation — no. (%)	48 (14.2)	11 (3.2)	0.20 (0.10–0.39)	<0.001
Hematoma requiring evacuation — no. (%)	9 (2.7)	2 (0.6)	0.21 (0.05–1.00)	0.03
Secondary outcomes				
Death from any cause — no. (%)	0	4 (1.2)		0.12
Pneumothorax — no. (%)	1 (0.3)	1 (0.3)		1.00
Hemothorax — no. (%)	0	0		—
Cardiac tamponade — no. (%)	1 (0.3)	0		0.50
Transient ischemic attack — no. (%)	0	1 (0.3)		1.00
Stroke — no. (%)	0	1 (0.3)		0.50
Non-CNS embolism — no. (%)	0	0		—
Deep-vein thrombosis — no. (%)	0	0		—
Pulmonary embolism — no. (%)	0	0		—
Valve thrombosis — no. (%)	0	0		—
Lead dislodgement — no. (%)	4 (1.2)	1 (0.3)		0.21
Superficial wound infection — no. (%)	3 (0.9)	1 (0.3)		0.37
Infection related to device system — no. (%)	6 (1.8)	2 (0.6)		0.17
Myocardial infarction — no. (%)	1 (0.3)	0		0.50
Patient-satisfaction score†	5.9±1.8	6.4±1.5		<0.001



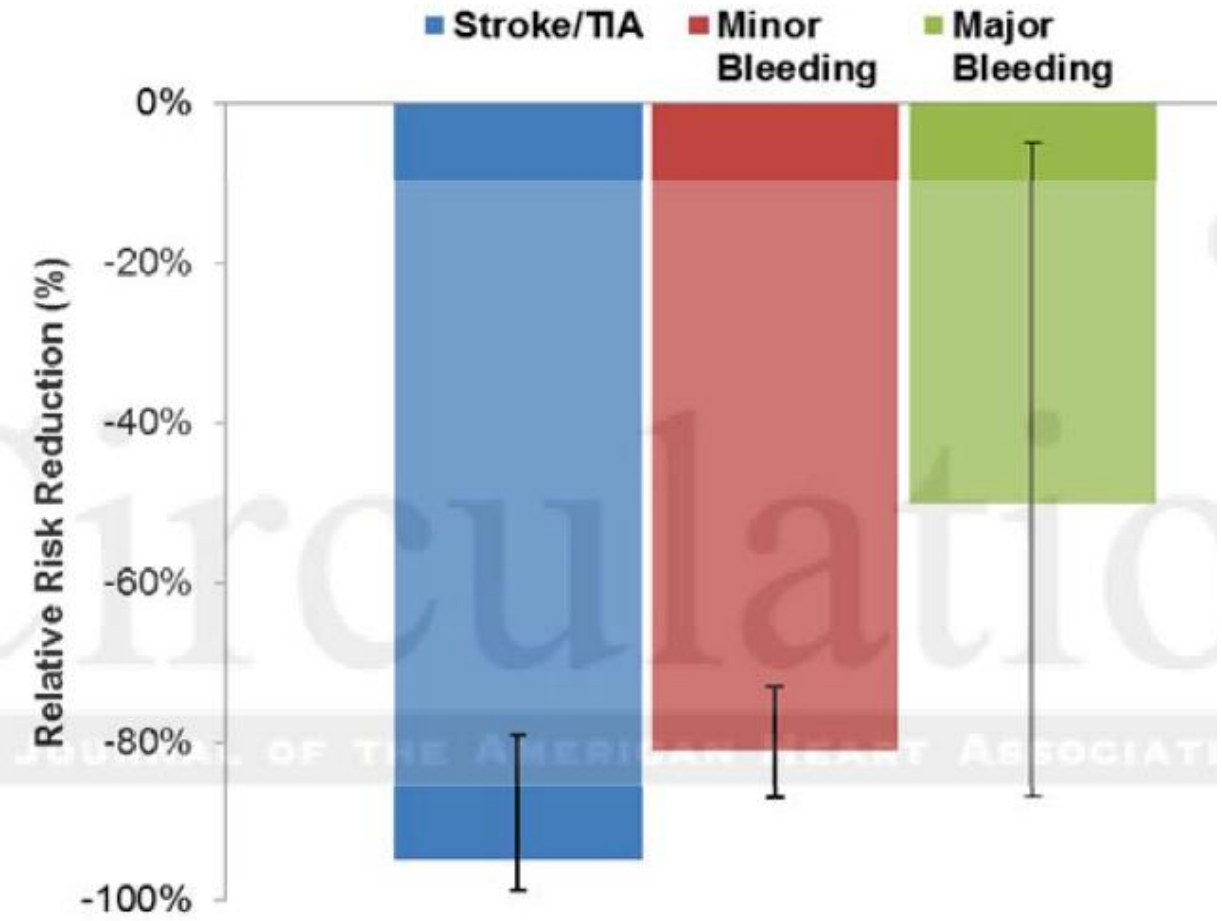
ACC Middle East Conference 2017

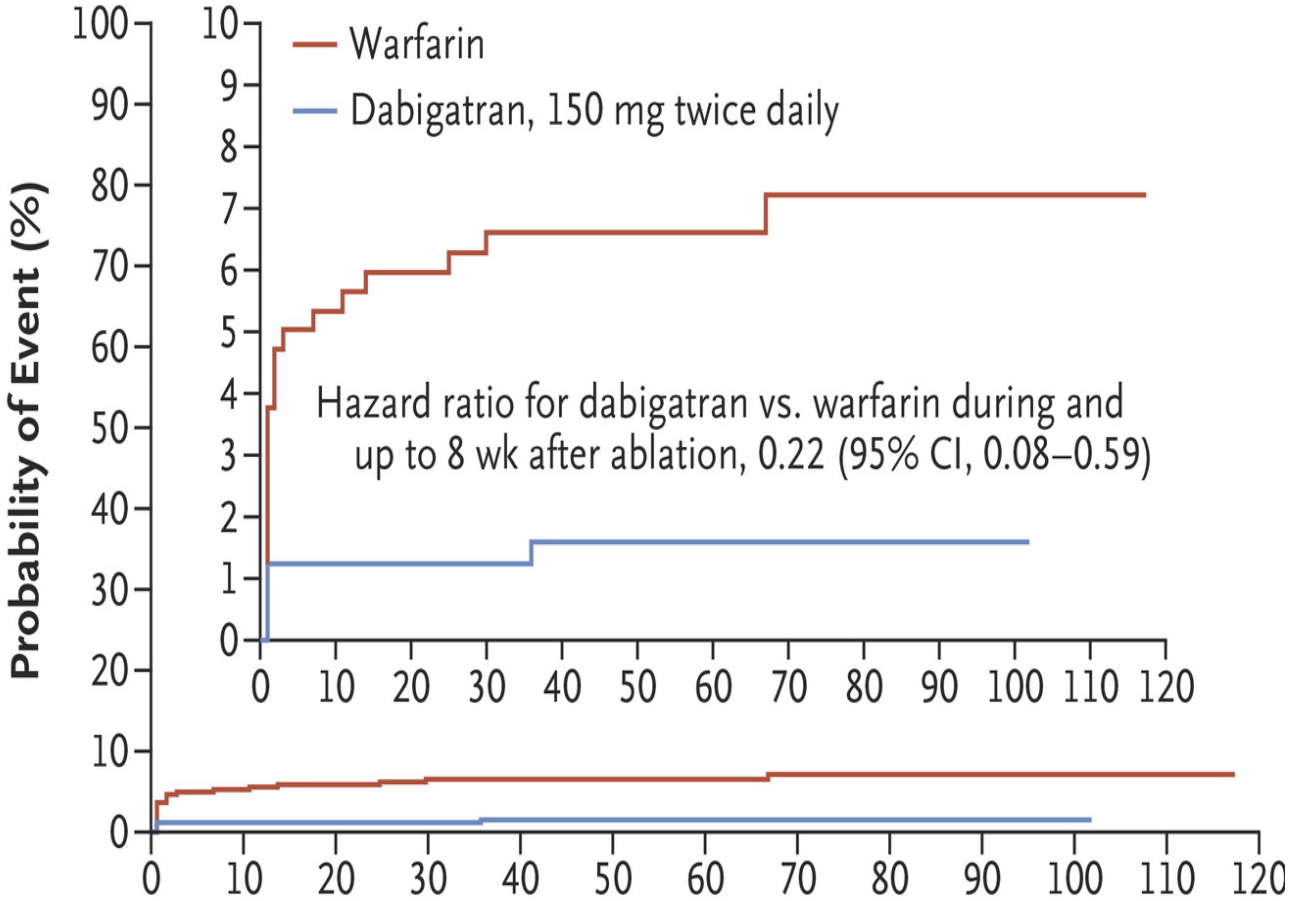
Birnie et al *N Engl J Med* 2013; 368:2084-2093

Peri-AF-Ablation anticoagulation

COMPARE: uninterrupted warfarin better than low-molecular weight heparin

RE-CIRCUIT: uninterrupted dabigatran better than uninterrupted warfarin



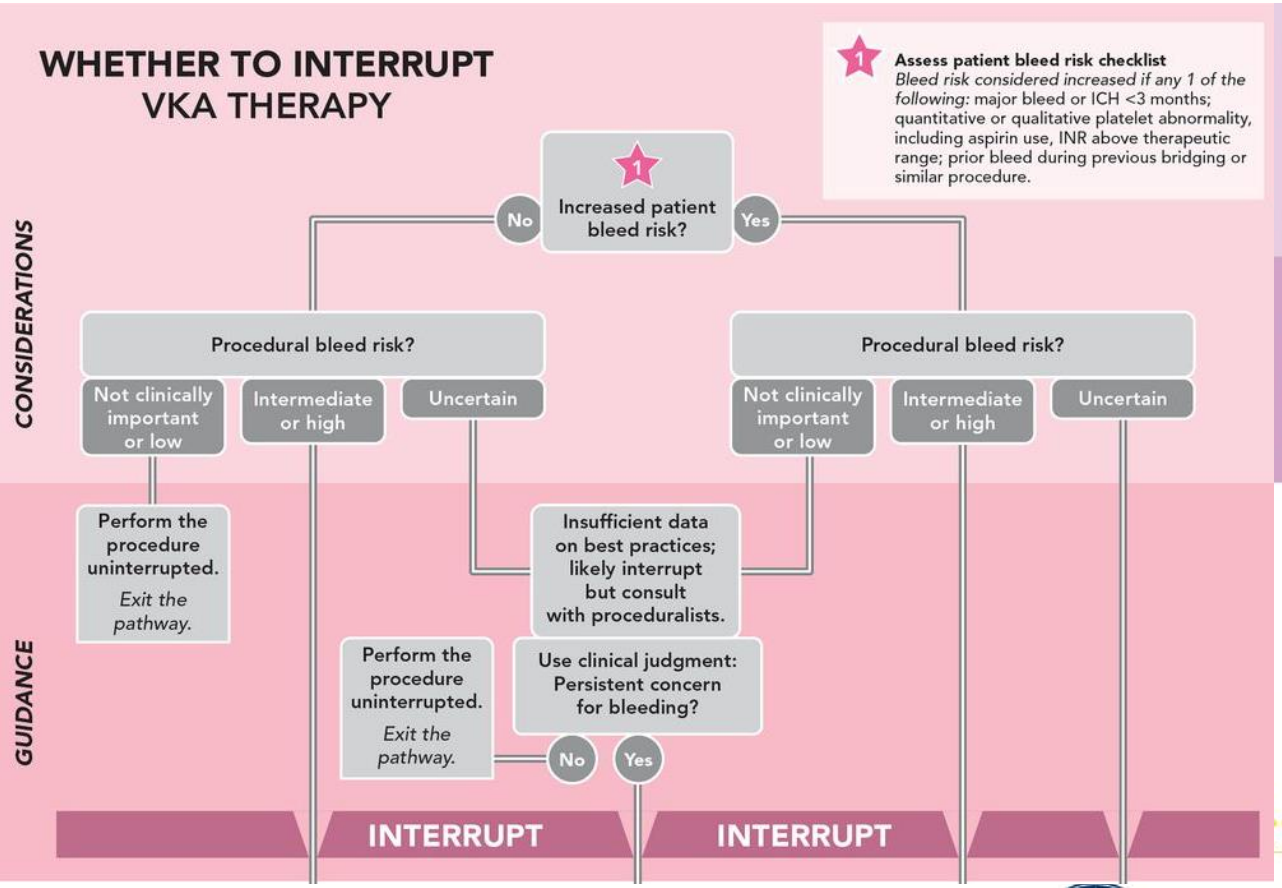


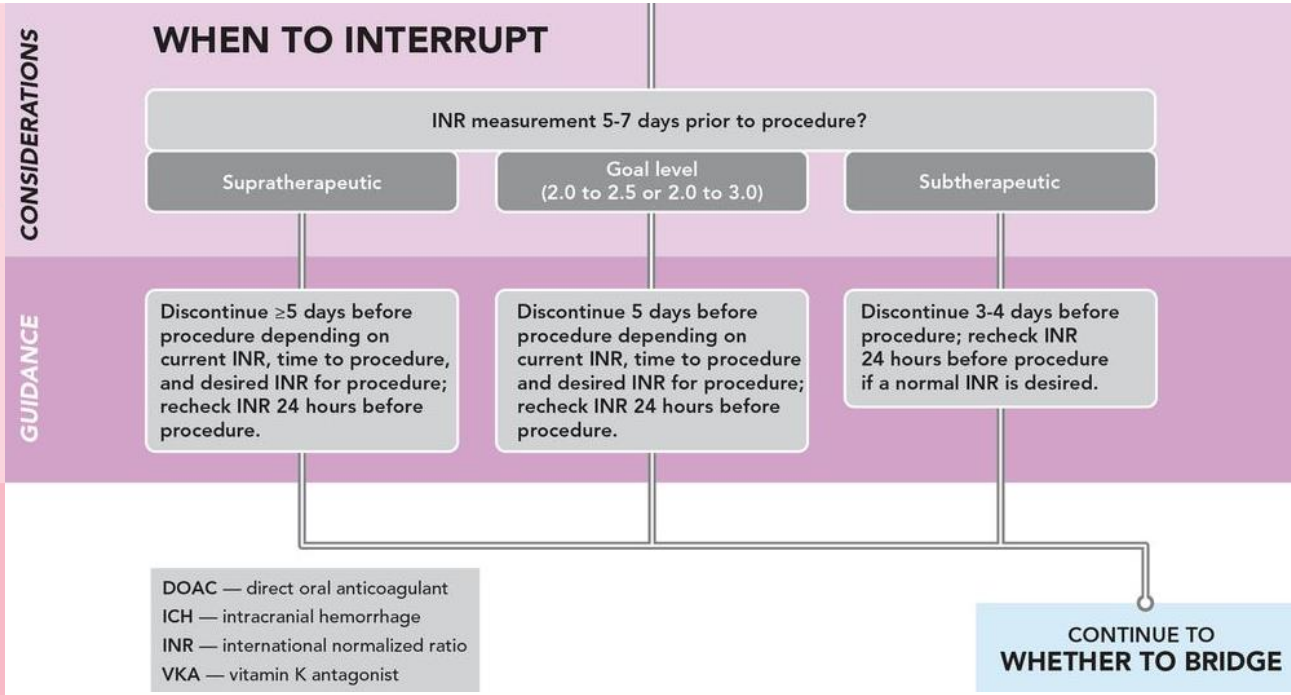
DI Biase et al *Circulation* 2014: **129**:2638–2644

Calkins et al *N Engl J Med* 2017; 376:1627-1636

ACC Middle East Conference 2017

Interrupting VKA antagonists
ACC expert consensus





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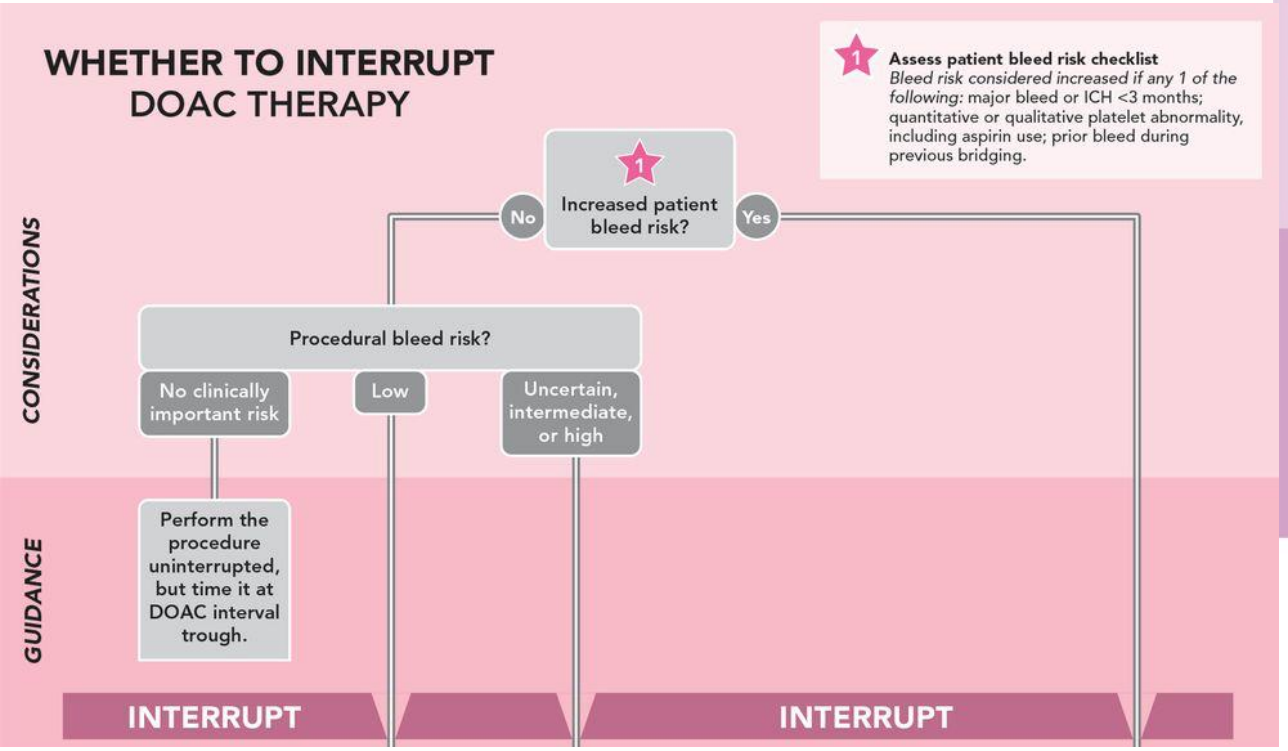
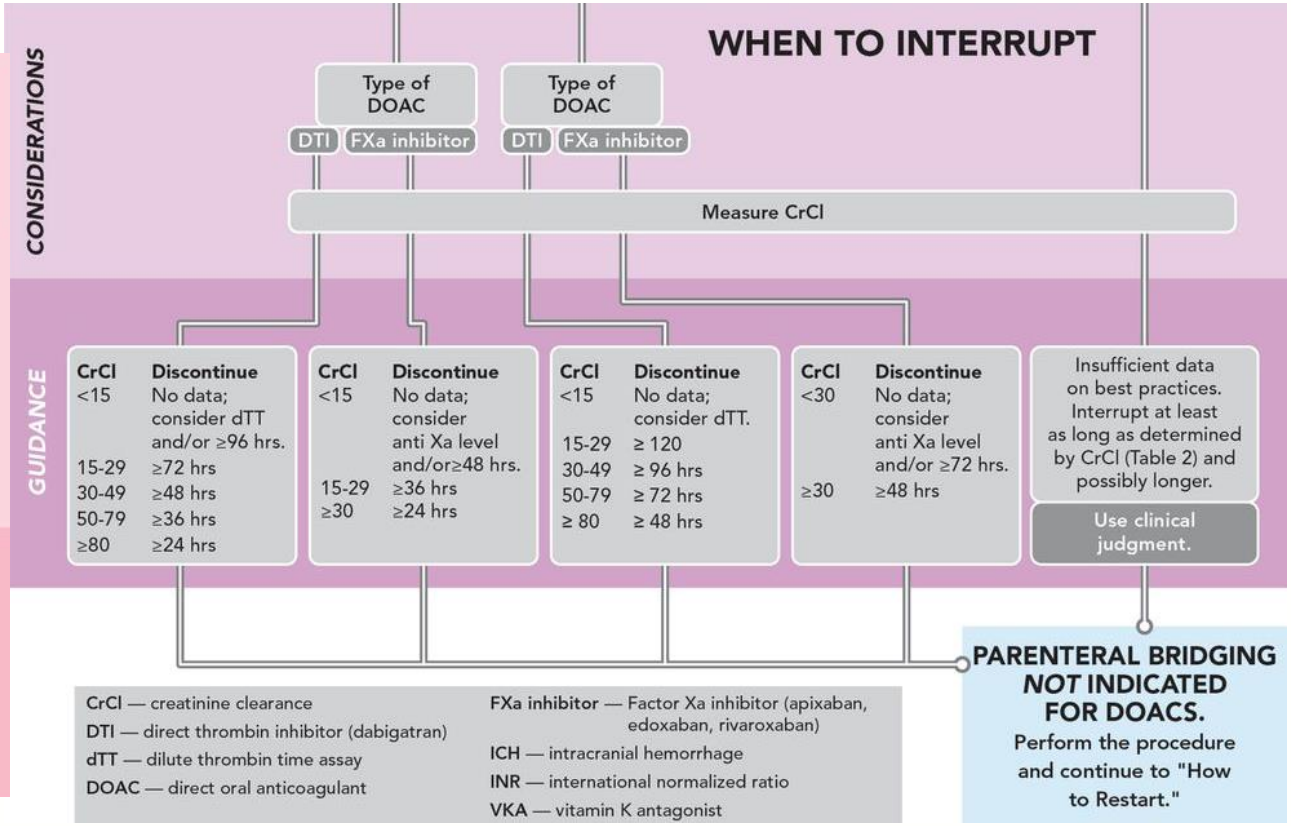
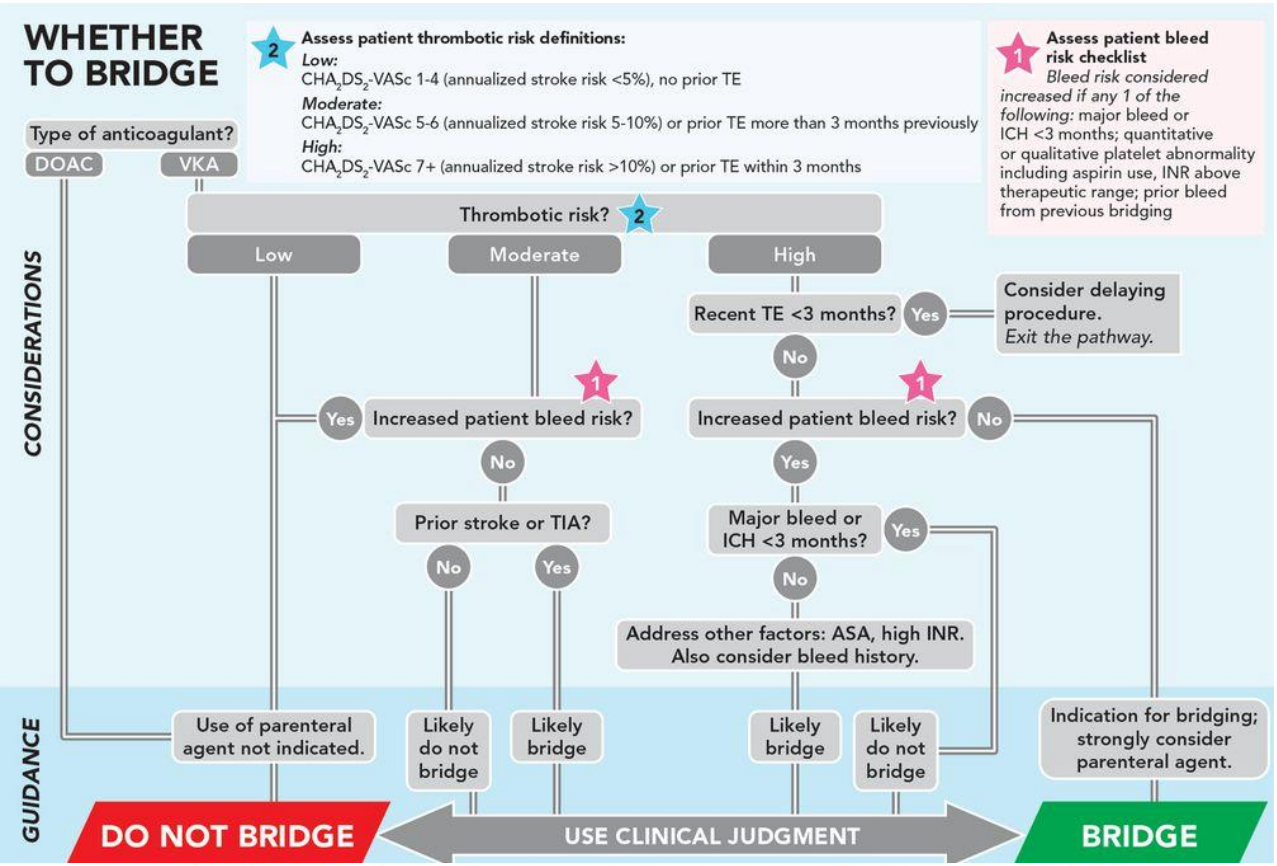
Interrupting Direct Oral Anticoagulants
ACC expert consensus

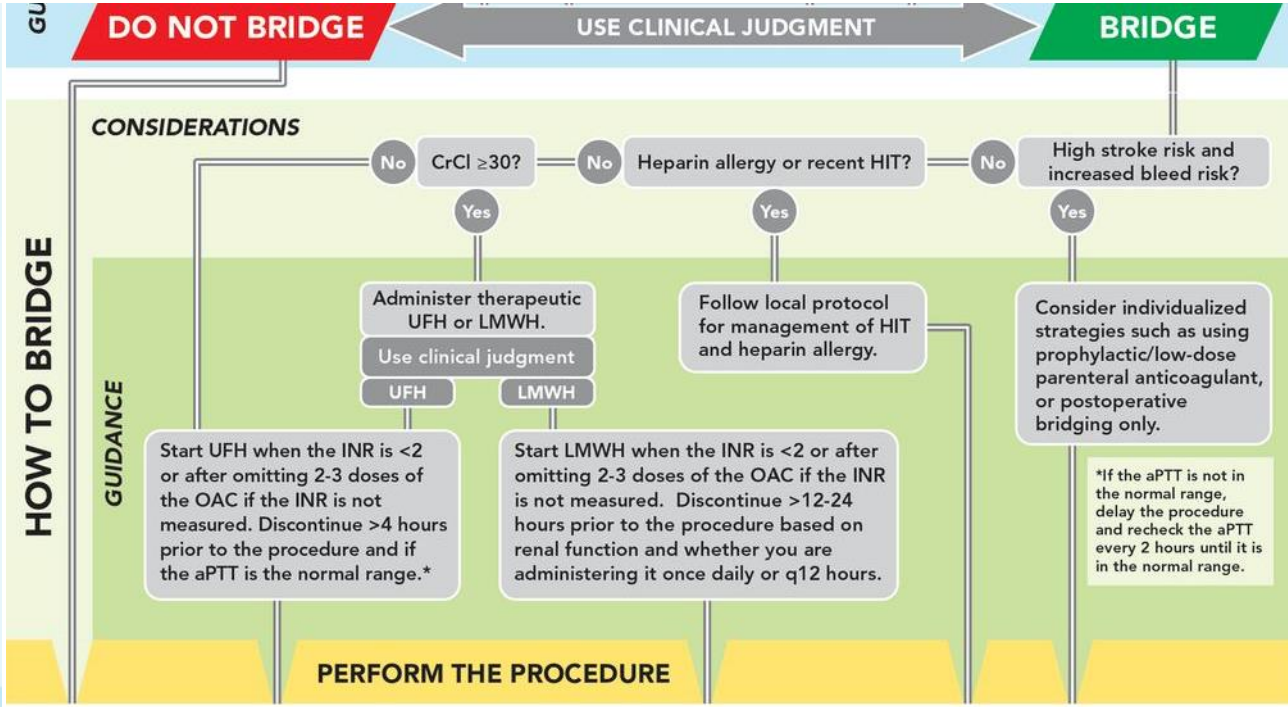




guidelines recommend discontinuing a DOAC prior to neuraxial procedures (for 4 to 5 days for dabigatran and 3 to 5 days for factor Xa inhibitors), with reinitiation 24 hours postprocedure

Bridging Periprocedural anticoagulation *ACC expert consensus*





aPTT – activated partial thromboplastin time assay; **ASA** – acetylsalicylic acid (aspirin); **DOAC** – direct oral anticoagulant; **HIT** – heparin-induced thrombocytopenia; **ICH** – intracranial hemorrhage; **INR** – international normalized ratio; **LMWH** – low-molecular-weight heparin; **OAC** – oral anticoagulation; **TE** – thromboembolic event; **TIA** – transient ischemic attack; **UFH** – unfractionated heparin; **VKA** – vitamin K antagonist

Bridging in Non-Valvular AF:*BRIDGE trial*

Table 2. Perioperative Anticoagulant Management.

Variable	No Bridging (N=950)	Bridging (N=934)	P Value
Warfarin treatment			
Preprocedure time not taking warfarin			0.28
No. of patients with data	872	839	
Mean — days	5.2±1.4	5.3±1.8	
Time to first postprocedure warfarin dose			0.40
No. of patients with data	735	696	
Mean — days	1.5±1.3	1.4±1.0	
Low-molecular-weight heparin or placebo			
Preprocedure dose			0.61
No. of patients with data	796	768	
Mean no. of doses	5.0±0.7	5.0±1.4	
Patients in whom the last dose was taken on the morning of the day before the procedure — no./total no. (%)	778/796 (97.7)	734/768 (95.6)	0.02
Time to first postprocedure dose			
Major surgery or procedure (high bleeding risk)			0.74
No. of patients with data	235	223	
Mean — hr	53.3±31.6	51.3±27.9	
Minor surgery or procedure (low bleeding risk)			0.74
No. of patients with data	526	497	
Mean — hr	21.1±2.3	21.0±2.4	
Postprocedure dose			0.47
No. of patients with data	764	721	
Mean no. of doses	15.7±7.4	16.1±8.4	
Aspirin treatment — no./total no. (%)			0.53
Interruption ≥7 days before procedure	92/324 (28.4)	92/329 (28.0)	
Interruption <7 days before procedure	41/324 (12.7)	33/329 (10.0)	
No interruption	191/324 (59.0)	204/329 (62.0)	

Table 3. Study Outcomes.

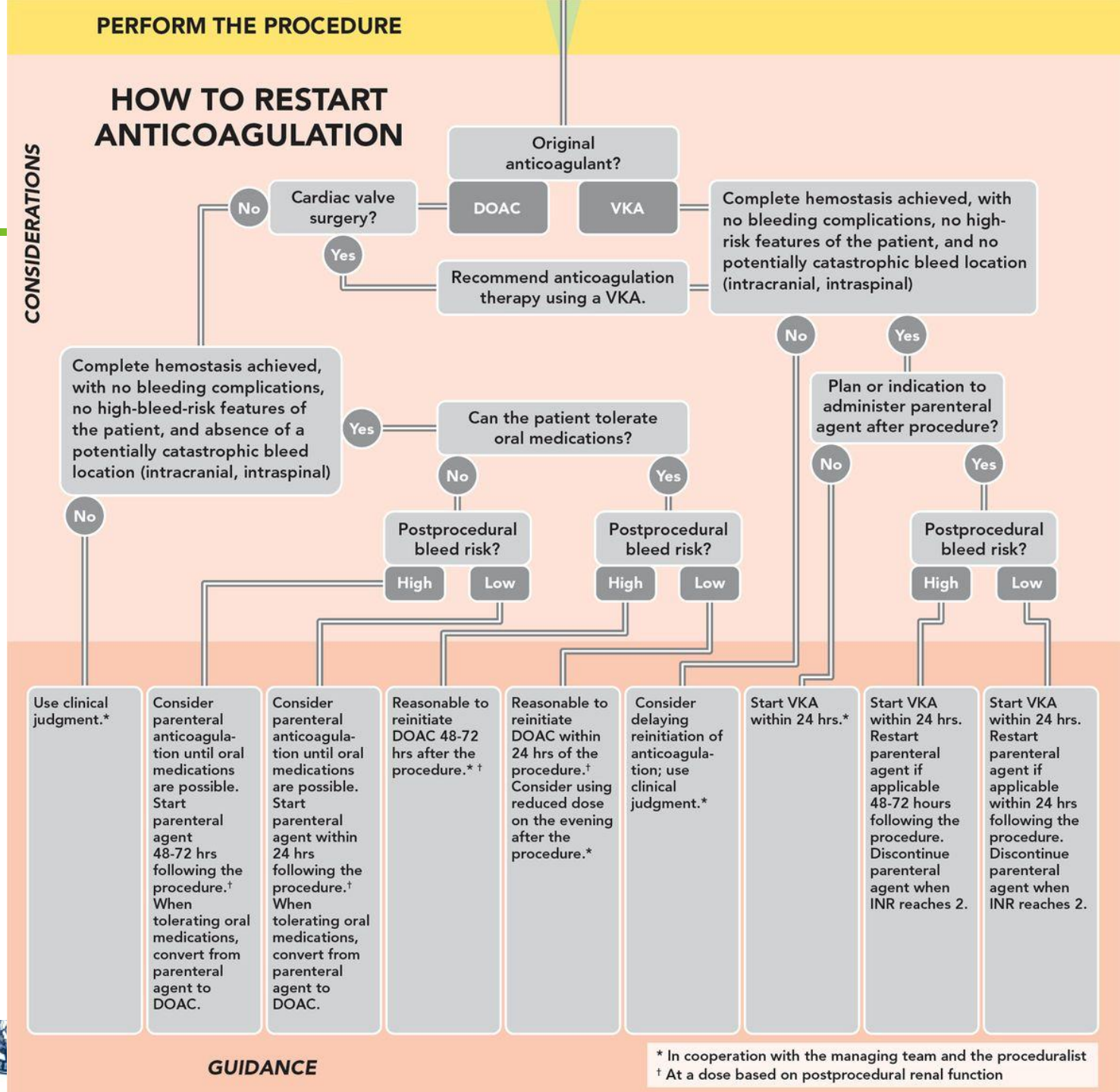
Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

N Engl J Med **373**:823–833

Re-Initiating anticoagulation *ACC expert consensus*

1. Establish that hemostasis has been achieved
2. If lower postprocedural risk of bleeding, therapeutic parenteral anticoagulation, if indicated, can be started within the first 24 hours
3. If higher postprocedural risk of bleeding, therapeutic parenteral anticoagulation should be delayed for at least 48 to 72 hours after the procedure.
4. If VKA therapy is reinitiated, careful monitoring of the INR during bridging is required to mitigate bleed risk.
5. LMWH or UFH should be discontinued when the INR is within goal range (≥2.0). This approach is modified if argatroban.



Conclusions

- Risk of stroke needs to be individualized in patient with AF
- Oral anticoagulation reduces stroke in patients at risk
- NOACs provide superior outcomes compared with warfarin
  - Particularly reduced hemorrhagic stroke
  - Particularly reduced CNS bleeds
- Periprocedural management requires complex procedural and patient risk assessment: