Newer Anticoagulants

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Learning Objectives

- After the talk, the attendees will:
- 1. Be aware of the 3 new oral anticoagulants and their mechanisms of action;
- 2. Know the efficacy and safety benefits of these 3 agents compared to warfarin;
- 3. Understand that these agents are effective in all age groups; and
- 4. Know the indications for use of these agents and the situations where there are not enough data to recommend their use.

Atrial Fibrillation I

- Atrial fibrillation (Afib) affects about 2,700,000 Americans.
- Patients with Afib, on the average, have 5 times the risk of ischemic stroke as individuals without Afib. Independent of additional risk factors, the risk of stroke is about 5%/year.

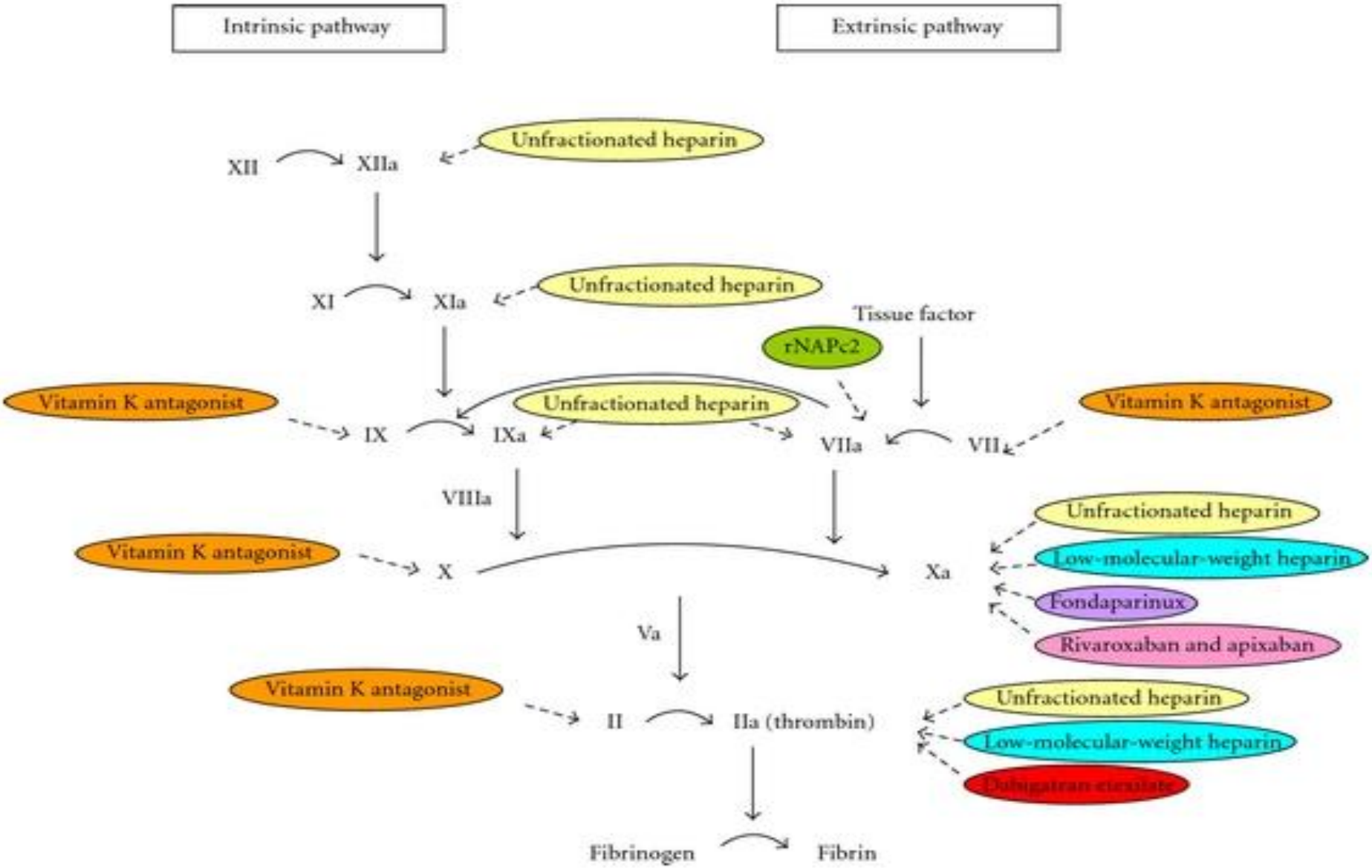
Atrial Fibrillation II

- CHADS2 Score

Risk Factor	Score
Prior Stroke or TIA	2
Age>75 years	1
Hypertension	1
Diabetes	1
Congestive Heart Failure	1

Atrial Fibrillation III

CHADS2 Score	Nonfatal Strokes per 1,000 patient years
0	8
1	22
2	45
3-6	96 (10%/year)


Intrinsic pathway
Extrinsic pathway
Unfractionated heparin
XII
XIIa
XI
XIa
Unfractionated heparin
Tissue factor
rNAPc2
Vitamin K antagonist
IX
IXa
Unfractionated heparin
VIIa
VII
Vitamin K antagonist
VIIIa
Unfractionated heparin
Low-molecular-weight heparin
Fondaparinux
Rivaroxaban and apixaban
Vitamin K antagonist
X
Xa
Va
Vitamin K antagonist
II
IIa (thrombin)
Unfractionated heparin
Low-molecular-weight heparin
Dabigatran etexilate
Fibrinogen
Fibrin

Warfarin I

- Warfarin acts by inhibiting Vitamin K dependent activation of clotting Factors II, VII, IX, X, and Proteins C and S.
- The INR (International Normalized Ratio) must be monitored in patients treated with warfarin. This can be as infrequently as monthly in stable patients without other medication changes. It may need to be monitored every few days during initiation of warfarin therapy, and when other medications, which may have interactions with warfarin, are changed.

Warfarin II

- Warfarin is dosed daily, but the dose may be different on different days of the week.
- Due to the long half lives of Protein S (30 hours), Factor X (36 hours) and Factor II (50 hours) and the wide inter-individual range of effective doses, attainment of stable therapeutic doses averages 44-59 days, depending on strategy and protocol; loss of effect takes 2-5 days after discontinuation.

Warfarin III

- Warfarin has multiple mechanisms for interaction with other drugs, and it should be assumed that any change in other medications may affect the INR.
- Warfarin effect may be decreased by high intake of Vitamin K containing foods (green leafy vegetables) or increased by very low Vitamin K intake.
- Use in the elderly is guided by monitoring the INR.

Warfarin IV

- Reversal of anticoagulation with warfarin can be achieved by low dose oral Vitamin K in 24-48 hours.
- Reversal can be achieved in a few hours by intravenous administration of fresh frozen plasma plus intravenous Vitamin K, or by use of clotting factor concentrates.

Warfarin and Afib[1]

- Treatment of patients, with sustained or paroxysmal Afib and a CHADS2 score >0, with warfarin decreases the risk of nonfatal stroke by 66% and the risk of all cause mortality by 28%.
- Warfarin markedly increases the risk of hemorrhagic stroke.

Emergency Hospitalization for Adverse Drug Events in Older Americans[2]

- There were an estimated 99,628 emergency hospitalizations/year in 2007-2009 in the US, due to adverse drug events in patients age >64. Forty-eight percent were in patients age >79.
- Warfarin was responsible for 33.3% of all of these hospitalizations (33,176 year).

Dabigatran etexilate (Pradaxa) I

- Dabigatran and its active metabolites are direct inhibitors of thrombin. They inhibit both conversion of fibrinogen to fibrin and thrombin-induced platelet aggregation.
- aPTT provides an approximation of dabigitran's anticoagulant effect. Thrombin time and other, less available, tests give more quantitative estimates.
- Dabigatran is dosed every 12 hours.

Dabigatran etexilate (Pradaxa) II

- Onset of effect is 1-2 hours.
- Disappearance of effect is 24-72 hours, depending on renal function.
- Elimination is 80% renal.
- The dose of dabigitran should be reduced from 150 mg BID to 75 mg BID in patients with eGFR <30 ml/min, and should be avoided in patients with eGFR <15 ml/min, due to lack of data in these patients.

Dabigatran etexilate (Pradaxa) III

- In elderly patients, dabigatran dosing should be adjusted for renal function.
- Dabigatran is not a substrate, inducer or inhibitor of CYP P450 enzymes.
- Dabigatran is a P-glycoprotein (Pgp) substrate and is affected by inducers and inhibitors of Pgp.
- Inducers of Pgp activity include rifampin.
- Inhibitors of Pgp include amiodarone, dronedarone, ketoconazole, verapamil, and quinidine.

Dabigatran etexilate (Pradaxa) IV[4]

- A specific antibody fragment for dabigatran reversal has been highly effective in Phase I trials.
- Recombinant Factor VIIa and activated prothrombin complex may be effective for reversal of bleeding due to dabigatran.
- Prior to elective operations or invasive procedures, dabigatran should be discontinued for 1-2 days in patients with eGFR >50 and 3-5 days in patients with eGFR <50.

Rivaroxaban (Xarelto) I

- Rivaroxaban acts by inhibiting Factor Xa.
- Onset of effect is 2-4 hours.
- Disappearance of effect is 24-48 hours depending on renal function.
- Rivaroxaban is dosed QD with food at 20 mg for patients with eGFR >50 ml/min and 15 mg for patients with eGFR 15-50 ml/min
- Use of rivaroxaban in patients with eGFR <15 ml/min should be avoided, due to lack of data in this group.

Rivaroxaban (Xarelto) II

- Rivaroxaban is a substrate for Pgp and Cyp 3A4/5.
- Activity may be decreased by inducers of Pgp and Cyp 3A4/5, such as rifampin and phenytoin.
- Activity may be increased by inhibitors of Pgp and Cyp 3A4/5, such as ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole.
- Bioavailability is markedly increased in patients with significant liver disease.
- Dosing in the elderly should be adjusted based on renal function.

Rivaroxaban (Xarelto) III

- Activated prothrombin complex concentrate and four factor prothrombin complex concentrate may be useful in reversal of rivaroxaban-induced bleeding.
- Rivaroxaban should be discontinued for at least 24 hours prior to operations or invasive procedures.

Apixaban (Eliquis) I

- Apixaban acts by inhibiting Factor Xa.
- It is dosed every 12 hours at 5 mg in most patients.
- It is dosed at 2.5 mg in patients with at least 2 of: age >80, weight < 60 Kg (132 lbs), serum creatinine >1.4 mg/dl.
- The onset of effect is 2-4 hours.
- Disappearance of effect is 24-48 hours.
- There are no good data on reversal of bleeding.

Apixaban (Eliquis) II

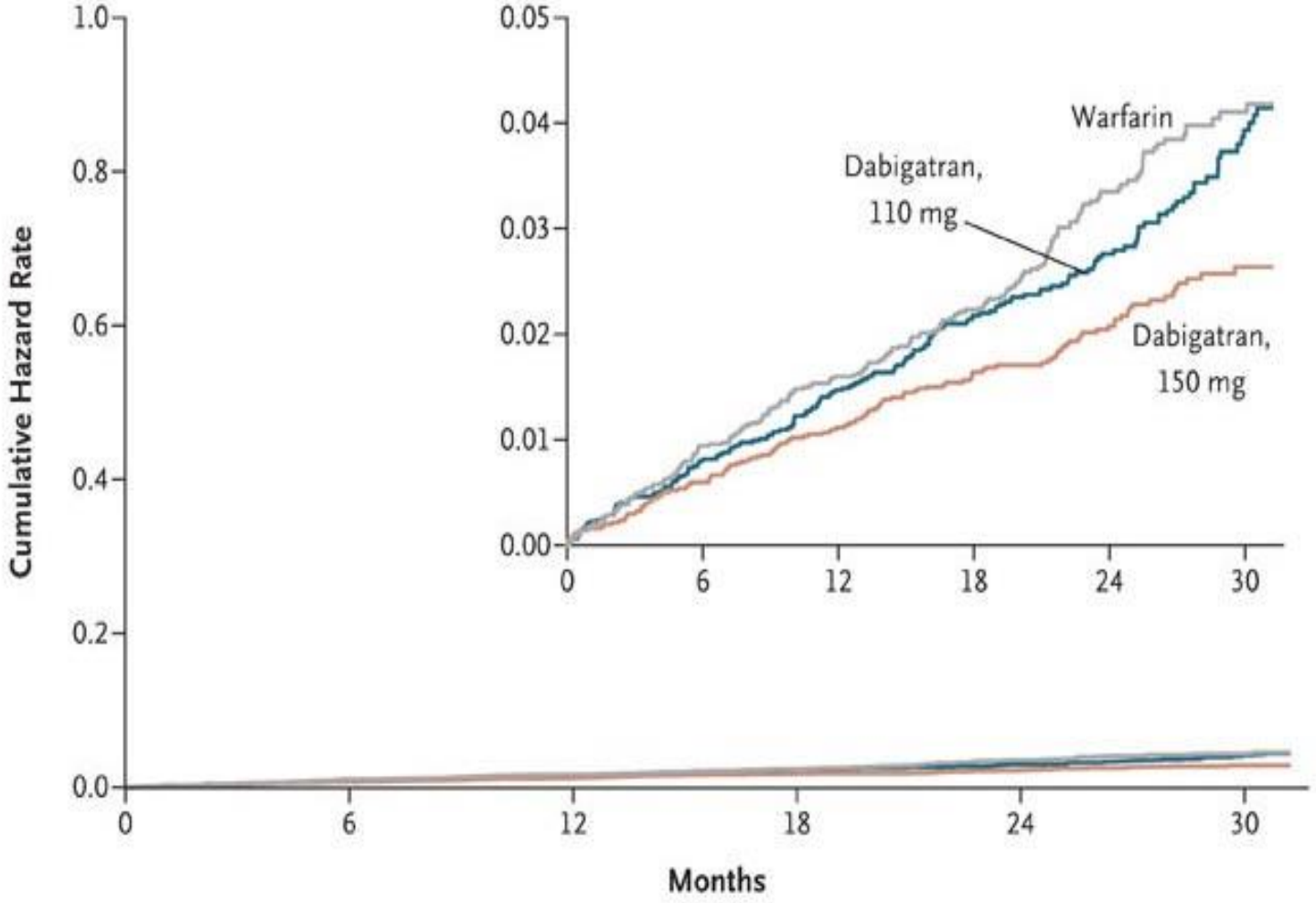
- Renal excretion only accounts for 27 percent of total clearance.
- Effects of moderate hepatic impairment on apixaban clearance are unclear.
- Apixaban is a substrate for both Pgp and Cyp 3A4/5.
- Clearance is decreased by strong inhibitors of both Pgp and Cyp 3A4/5, such as rifampin and phenytoin.

Apixaban (Eliquis) III

- Clearance is decreased by strong inhibitors of both Pgp and Cyp 3A4/5, such as rifampin and phenytoin.
- Clearance is increased by strong inducers of both Pgp and Cyp 3A4/5, such as ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole.
- Prior to operations or invasive procedures, apixaban should be discontinued for 24 hours for low risk procedures and for 48 hours for moderate or high risk procedures.

Dabigatran vs warfarin in Non-valvular Atrial Fibrillation(NVAF)[7]

- Prospective, randomized, open label, blinded endpoint.
- Three arms; two fixed doses of dabigatran (110 and 150 mg) and adjusted warfarin.
- N = 18,113 (6,028/arm), Mean age 71.5, 40% >74.
- Follow-up 1-3 years.
- Mean CHADS2 Score = 2.1
- Primary efficacy outcome: stroke or systemic embolism.
- Primary safety outcome: major bleeding.



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

RE-LY Outcomes

	D	W	RR	P
Primary	134	199	.66	<.001
Ischemic CVA	103	134	.75	<.05
Hemorrhagic CVA	12	45	.26	<.001
MI	89	63	1.38	.048
Vascular Mortality	274	317	.85	.04
Total Mortality	438	487	.88	.051

RE-LY Primary Outcome by Age

Age	D (%/year)	W(%/year)	RR	P
<65	.69	1.35	.51	<.05
65-74	.98	1.45	.68	<.05
>74	1.43	2.15	.67	<.05

RE-LY Safety and Net Outcomes

	D	W	HR	P
MB	375	397	.93	.31
LTMB	175	212	.81	.04
GIMB	182	120	1.50	<.001
ICB	36	87	.40	<.001
Net Outcomes	832	901	.91	.04

- Net Outcomes = stroke + systemic embolism + myocardial infarction + death + major bleeding

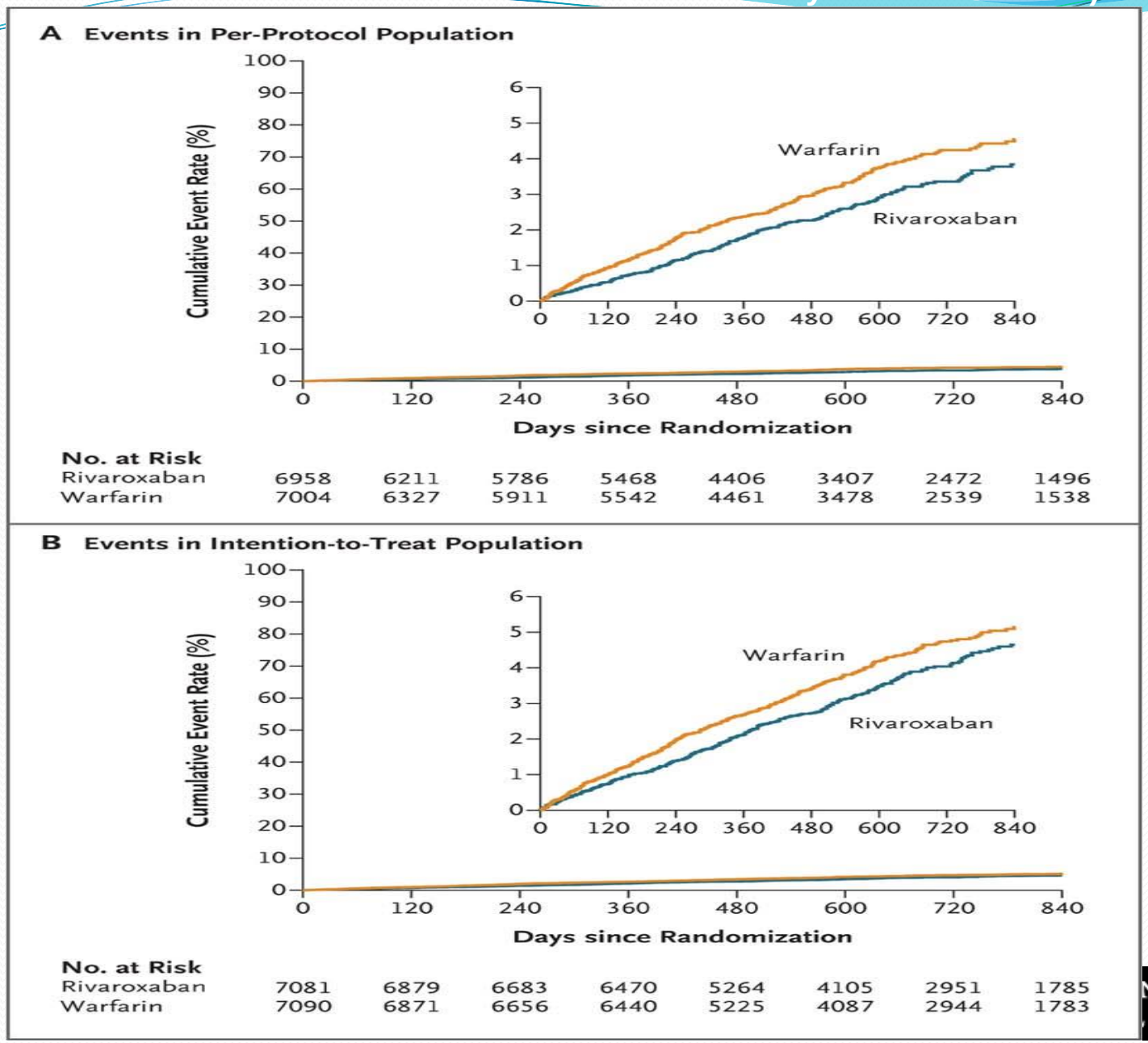
RELY Safety Endpoints by Age

Age	D	W	HR	P
Major Bleeding %/yr				
<75	2.12	3.04	.70	<.05
>74	5.10	4.37	1.18	NS
GI Bleeding %/yr				
<75	1.22	1.03	1.19	NS
>74	2.80	1.59	1.79	NS
Intracranial bleeding %/yr				
<75	0.26	0.61	0.43	<.05
>74	0.41	1.00	0.42	<.05

Rivaroxaban vs warfarin in non-valvular Atrial Fibrillation

- Prospective, randomized, open label, blinded endpoint.
- Two arms; fixed dose of rivaroxaban (20 or 15 mg adjusted for eGFR) and adjusted warfarin.
- N = 14,264 (7,132/arm), median age 73, 38% >75.
- Median Follow-up 707 days.
- Mean CHADS2 Score = 3.47
- Primary efficacy outcome: stroke or systemic embolism.
- Primary safety outcome: major and clinically relevant non-major bleeding.

Cumul… …int (Stroke or Systemic Embolism) in the Per-



ROCKET-AF Outcomes

	R	W	RR	P
Primary	269	306	.88	NS
Ischemic CVA	206	208	.994	NS
Hemorrhagic CVA	33	57	.58	.02
MI	101	126	.81	.12
Vascular Mortality	170	193	.89	.294
Total Mortality	208	250	.85	.07

ROCKET-AF Primary Outcome by Age

Age	D	W	RR	P
<75	144	152	.95	NS
>74	125	154	.80	NS

ROCKET-AF Safety

	R	W	HR	P
MB	375	397	.93	.31
Critical B	175	212	.81	.04
GIB	224	154	1.45	<.001
ICB	55	84	.67	.02
FB	27	55	.50	.003

ROCKET-AF Primary Safety Endpoint by Age

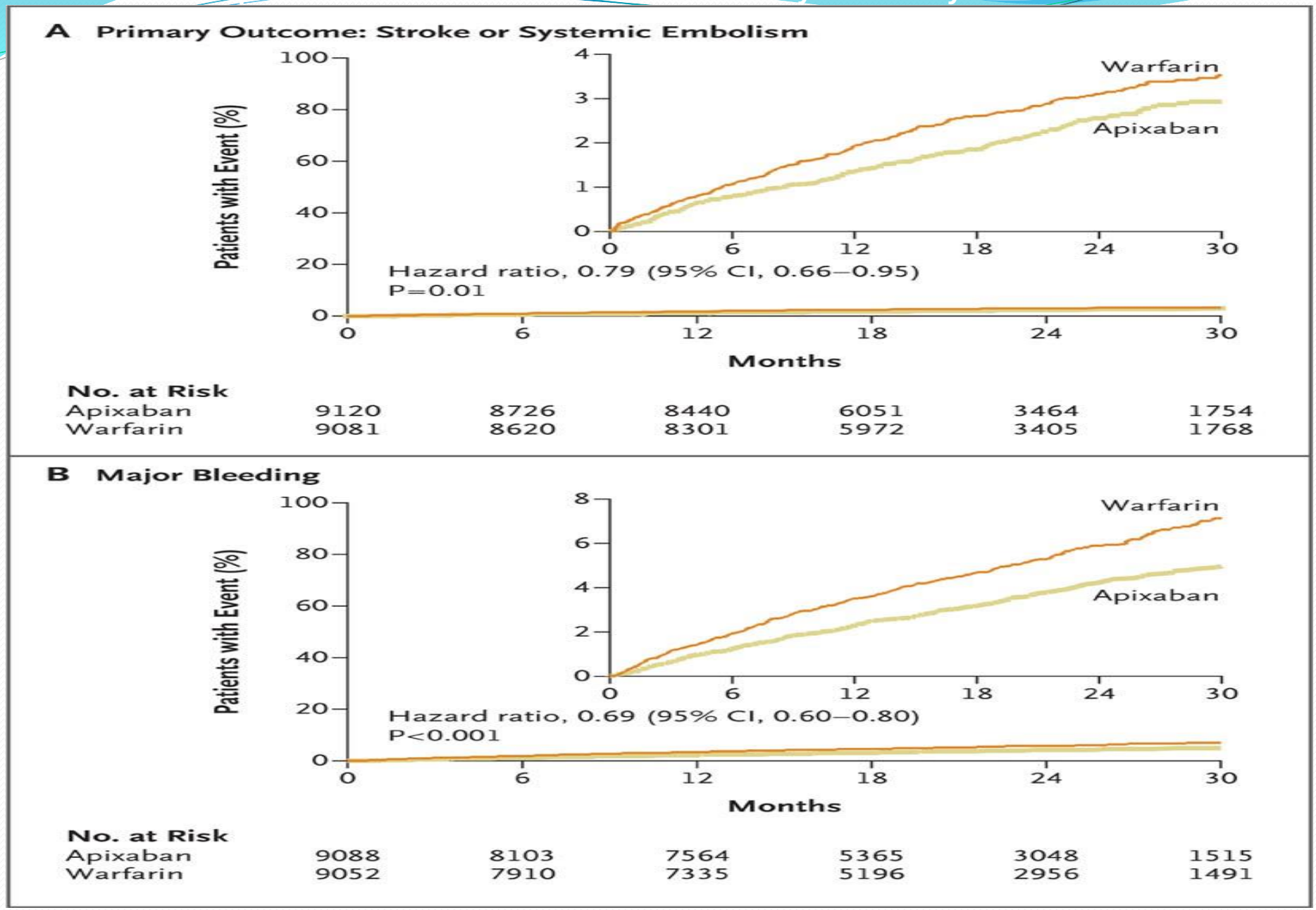
Age	R	W	HR	P
<65	241	260	.93	NS
65-75	541	556	.98	NS
>75	693	633	1.12	NS

- Primary Safety Endpoint = Major and Non-Major Clinically Relevant Bleeding

Apixaban vs warfarin in non-valvular Atrial Fibrillation

- Prospective, randomized, open label, blinded endpoint.
- Two arms; Fixed doses of apixaban 5 or 2.5 mg BID (adjusted for age, weight and renal function) and adjusted warfarin.
- N = 18,201 (9,100/arm), median age 70, 31% >74.
- Median Follow-up 1.8 years.
- Mean CHADS2 Score 2.1
- Primary efficacy outcome: stroke or systemic embolism.
- Primary safety outcome: major bleeding.

...mary Efficacy and Safety Outcomes.



ARISTOTLE Outcomes

	A	W	RR	P
Primary	212	265	.79	.01
Ischemic Stroke	162	175	.92	.42
Hemorrhagic Stroke	40	78	.51	<.001
MI	90	102	.61	.37
CV Mortality	1.88%/yr	2.02%/yr	.89	>.05
Total Mortality	603	669	.89	.047

ARISTOTLE Primary Outcome by Age

Age	A (%/yr)	W (%/yr)	RR	P
<65	1.0	0.9	1.1	NS
65-74	1.3	1.7	.76	<.05
>74	1.6	2.2	.73	<.05

ARISTOTLE Safety and Net Outcomes

	A	W	HR	P
MB	327	462	.69	<.001
SB	80	172	.46	<.001
GIB	105	119	.89	.37
ICB	52	122	.42	<.001
Net Outcomes	1009	1168	.85	<.001

- Net Outcomes = stroke + systemic embolism + death + major bleeding

ARISTOTLE Primary Safety Endpoint by Age

Age	R (%/yr)	W (%/yr)	HR	P
<65	1.2	1.5	.80	NS
65-75	2.0	2.8	.71	<.05
>75	3.3	5.2	.57	<.05

- Primary Safety Endpoint = Major Bleeding

SUMMARY I

- Dabigatran is easier to use than warfarin and has less interactions with other drugs and foods.
- In patients with NVAF, dabigatran is less effective than warfarin in preventing myocardial infarction, but more effective in preventing stroke or systemic embolism, ischemic stroke, hemorrhagic stroke and vascular mortality, and is borderline more effective in preventing total mortality.

SUMMARY II

- Compared to warfarin, dabigatran causes more GI bleeding, but less major bleeding and intracranial bleeding.
- Dabitran is more effective than warfarin, *in patients of all ages*, in preventing stroke or systemic embolism, and has a net clinical benefit *in patients of all ages*.

SUMMARY III

- In patients age <75, compared to warfarin, dabigatran causes numerically more GI bleeding, but significantly less major bleeding and intracranial bleeding.
- In patients age >74, compared to warfarin, dabigatran causes significantly more GI bleeding, and numerically more major bleeding, but significantly less intracranial bleeding.

SUMMARY IV

- In patients with NVAF, rivaroxaban is easier to use than warfarin and has less interactions with other drugs and foods.
- Rivaroxaban is numerically superior and statistically non-inferior to warfarin in preventing stroke or systemic embolism and statistically superior in preventing hemorrhagic stroke.

SUMMARY V

- Compared to warfarin, rivaroxaban causes more episodes of GI bleeding, but fewer episodes of major and clinically relevant bleeding, intracranial bleeding and fatal bleeding.
- Compared to those treated with warfarin, *patients of all ages* treated with rivaroxaban, have numerically fewer strokes or systemic embolism.
- Compared to those treated with warfarin, *patients of all ages* treated with rivaroxaban, have numerically fewer episodes of major and non-major clinically relevant bleeding.

SUMMARY VI

- In patients with NVAF, apixaban is easier to use than warfarin and has less interactions with other drugs and foods.
- Apixaban is superior to warfarin in preventing stroke or systemic embolism, hemorrhagic stroke and death from any cause.
- Compared to warfarin, apixaban causes fewer episodes of major bleeding, severe bleeding and intracranial bleeding.

SUMMARY VII

- Compared to those treated with warfarin, *patients over age 64,* who are treated with apixaban, have numerically fewer strokes or systemic embolism.
- Compared to those treated with warfarin, *patients over age 64,* who are treated with apixaban, have numerically fewer episodes of major bleeding.

CONCLUSIONS I
In patients with NVAF

- Compared to warfarin, newer anticoagulants (NA): dabigatran, rivaroxaban and apixaban, are easier to use and have fewer interactions with other drugs and foods.
- Compared to warfarin, NA are equally or more effective in preventing stroke or systemic embolism.

CONCLUSIONS II
In patients with NVAF

- NA are safe and effective at all ages.
- Despite no specific treatment for bleeding due to NA, in 50,578 patients in prospective, randomized clinical trials, compared to warfarin, NA caused no more episodes of major bleeding and significantly fewer episodes of intracranial bleeding.

Dabigatran vs warfarin in Patients with Mechanical Aortic or Mitral Valves[8]

- Prospective, randomized, open label, blinded endpoint.
- Two arms; dabigatran (adjusted to achieve trough dabigatran level of >.49 ng/ml) and adjusted warfarin.
- N = 252
- Follow-up 12 weeks.
- Stopped early due to excess thromboembolic and bleeding events in the dabigatran group.

Supplementary Slide I

- In patients with metal prosthetic aortic and mitral valves, warfarin is safer and more effective than dabigatran.
- In patients with eGFR <15 ml/min, warfarin is preferred to NA, due to lack of data with NA in these patients.
- In patients with mitral stenosis and atrial fibrillation, warfarin is preferred to NA, due to lack of data with NA in these patients

Supplementary Slide II

- In patients with Afib, NA are not recommended after intracoronary stent placement, due to lack of data with NA in these patients.
- In patients with Afib and ACS without stent placement, NA are not recommended, due to lack of data with NA in these patients.
- In patients with Afib prior to cardioversion, NA are not recommended, due to lack of data with NA in these patients.

Net Clinical Outcomes.

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

* The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. The net clinical outcome includes all efficacy outcomes through the cutoff date for the efficacy analysis and bleeding outcomes that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

† The comparison of the primary safety outcome of bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is in the hierarchical sequence preserving a type I error.

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...ke or Systemic Embolism.

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate	No. of Patients	No. of Events	Event Rate		Noninferiority	Superiority
			no./100 patient-yr			*no./100 patient-yr*			
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

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...leding Events.

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

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

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Outcomes.

Table 2. Efficacy Outcomes.*

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
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

* Analyses were performed on data from the intention-to-treat population and included all events through the cutoff date for efficacy outcomes of January 30, 2011; comparisons of the primary outcome and of death from any cause were analyzed as part of hierarchical sequence testing (starting with testing the primary outcome for noninferiority, then the primary outcome for superiority, then major bleeding, and finally death from any cause), to control the type I error.

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