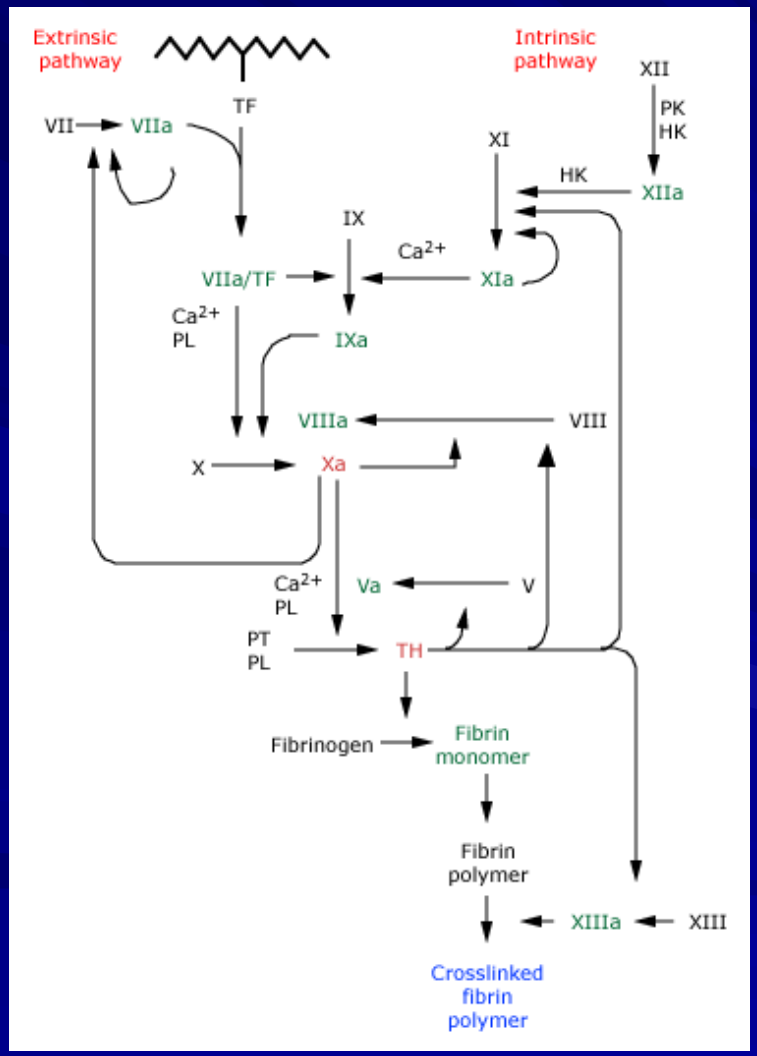
Antithrombin Agents:

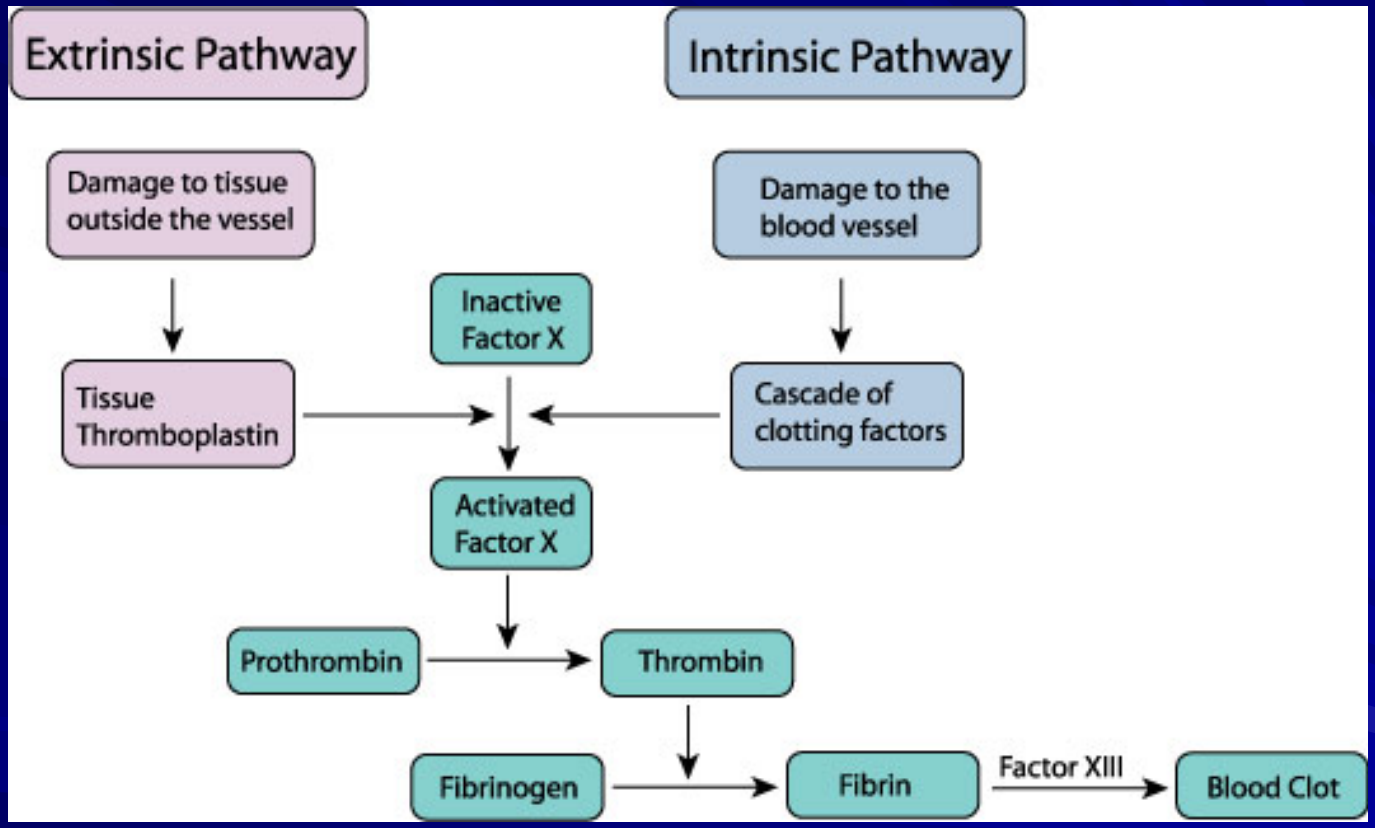
How are they changing management of thrombotic disorders?

Douglas Burtt, MD

Where does thrombin work?



Where does thrombin work?



How do we currently use Antithrombin drugs?

Table 17.15. Cardiovascular Uses of Antithrombotic Drugs

Drug	Chronic Angina	Unstable Angina/ NSTEMI	STEMI	DVT	Mechanical Heart Valve	Atrial Fibrillation	PCI	HIT
Platelet inhibitors								
Aspirin	+	+	+		(1)	(2)	+	
Thienopyridines		+	+				(3)	
GP IIb/IIIa antagonists		+	(4)				+	
Dipyridamole					(5)			
Anticoagulants								
UFH		+	+	+	(6)	(6)	+	
LMWH		+	+	+				
Direct thrombin inhibitors		(7)					+	+
Fondaparinux		(8)		+				
Warfarin			(9)	+	+	+		

(1) Sometimes used in combination with warfarin.

(2) If patient has a low risk of stroke, or if warfarin is contraindicated.

(3) When intracoronary stent is implanted.

(4) If PCI undertaken.

(5) Sometimes used in combination with warfarin for recurrent embolism.

(6) For hospitalized patients unable to take warfarin.

(7) If undergoing PCI.

(8) Emerging use.

(9) For 3–6 months after MI if large akinetic segment is present.

DVT, deep venous thrombosis; HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; NSTEMI, non-ST elevation myocardial infarction (MI); PCI, percutaneous coronary intervention; STEMI, ST-elevation MI; UFH, unfractionated heparin.

Patients with HIT

(or patients with history of HIT who require anti-coagulation)

- Argatroban
- Lepirudin, if there is hepatic impairment

Patients undergoing PCI

- Bivalirudin (Angiomax)
  - Rapid onset of action
  - Rapid elimination (half-life = 25 minutes)
  - Approved for PCI in unstable angina
  - Probably equivalent to Heparin plus GP IIb/IIIa inhibitor for primary PCI in STEMI, with a lower bleeding risk

Patients with Atrial Fibrillation or Atrial flutter

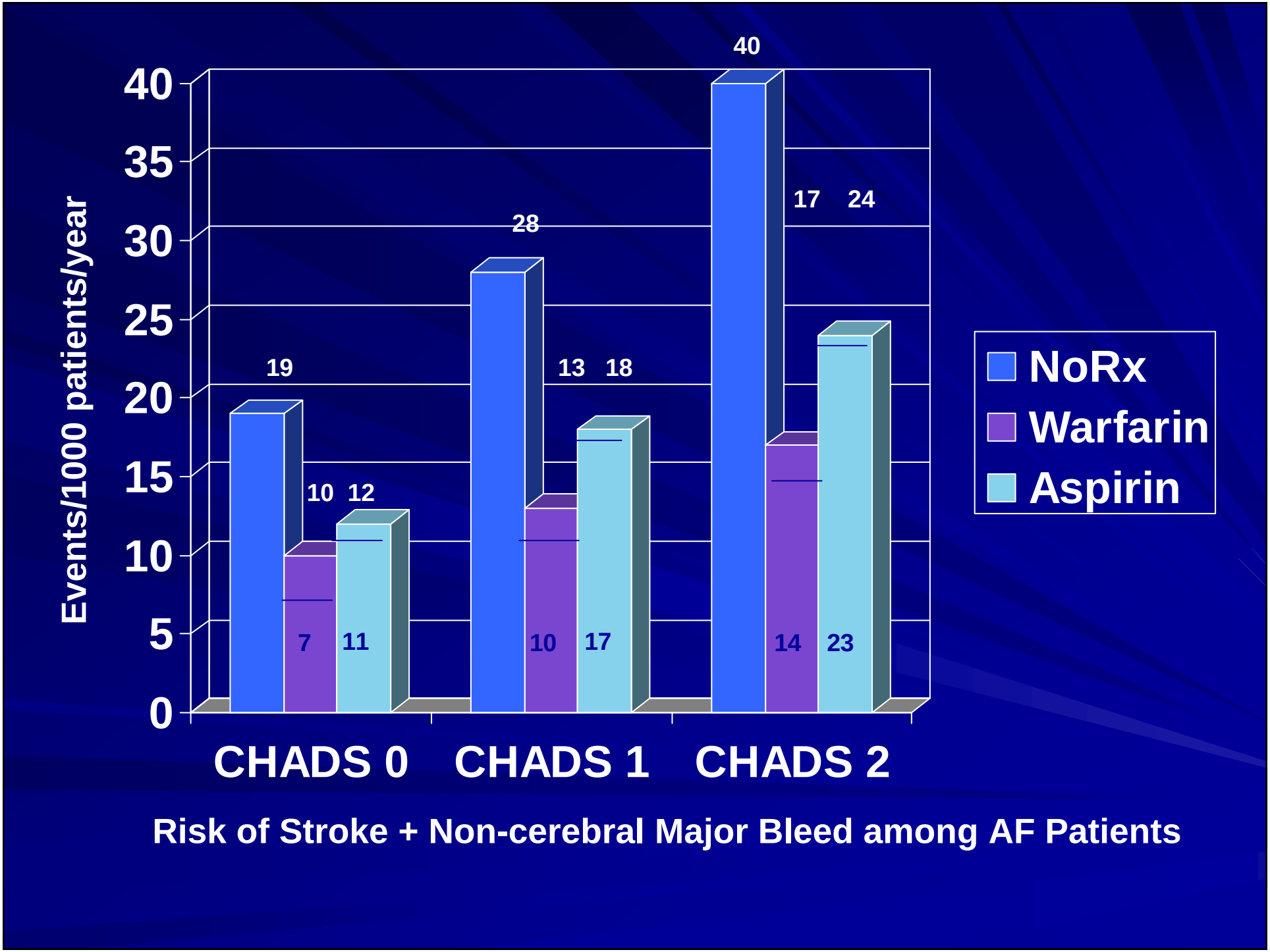
- Who do we treat with full AC?
  - CHADS2 score $\geq$ 2, without valvular disease
  - Any atrial fib, with significant valvular heart disease or prosthetic valve

In Canada – new CCS guidelines suggest use of oral AC (Warfarin or Dabigatran) for CHADS2 score of $\geq$ 1

CHADS2 score

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke/TIA/ Thromboembolism	2
Maximum Score	6

Patients (n = 1733)	Adjusted Stroke Rate (%/yr) 95% CI	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6



Risk of Stroke + Non-cerebral Major Bleed among AF Patients

Patients with Atrial Fibrillation or Atrial flutter

- Both a direct thrombin inhibitor, dabigatran (Pradaxa), and a factor Xa inhibitor, apixaban, have been shown to be as effective as Warfarin

Re-ly Trial

- > 18,000 patients randomized with :
  - Atrial fib within 6 months
  - At least one:
    - Previous stroke or TIA
    - LV ejection fraction < 40%
    - CHF (class II or >) within 6 months
    - Age ≥ 75
    - OR Age 65 – 74 with DM, HTN or CAD

Re-ly Trial

- Pts excluded for:
  - Severe heart valve disorder
  - Hx of severe stroke
  - Increased risks of bleeding
  - Creat clearance < 30
  - Active liver disease

Re-ly Trial

- Randomized to:
  - Warfarin
  - Dabigatran 150 mg BID
  - Dabigatran 110 mg BID

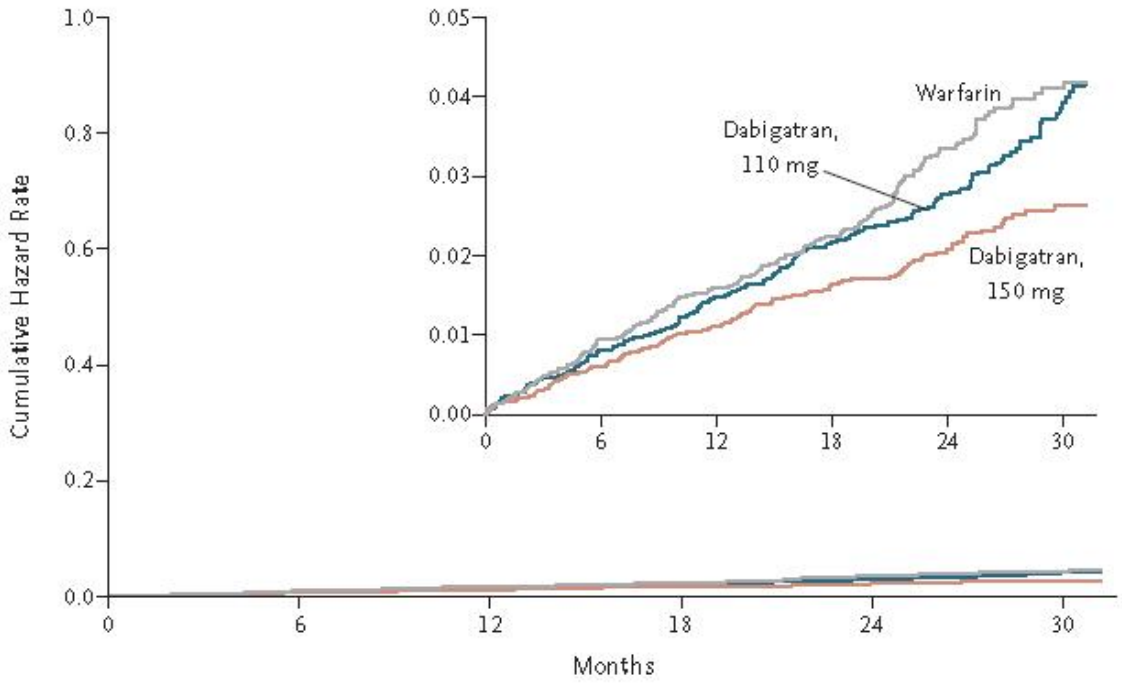
  - Followed for an average of 2 years

Re-ly Trial

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Characteristic	Dabigatran, 110 mg	Dabigatran, 150 mg	Warfarin
Age — yr	71.4±8.6	71.5±8.8	71.6±8.6
Weight — kg	82.9±19.9	82.5±19.4	82.7±19.7
Blood pressure — mm Hg			
Systolic	130.8±17.5	131.0±17.6	131.2±17.4
Diastolic	77.0±10.6	77.0±10.6	77.1±10.4
Male sex — no./total no. (%)	3865/6015 (64.3)	3840/6076 (63.2)	3809/6022 (63.3)
Type of atrial fibrillation — no./total no. (%)			
Persistent	1950/6011 (32.4)	1909/6075 (31.4)	1930/6021 (32.0)
Paroxysmal	1929/6011 (32.1)	1978/6075 (32.6)	2036/6021 (33.8)
Permanent	2132/6011 (35.4)	2188/6075 (36.0)	2055/6021 (34.1)
$CHADS_2$ score†	2.1±1.1	2.2±1.2	2.1±1.1
0 or 1 — no./total no. (%)	1958/6014 (32.6)	1958/6076 (32.2)	1859/6022 (30.9)
2 — no./total no. (%)	2088/6014 (34.7)	2137/6076 (35.2)	2230/6022 (37.0)
3–6 — no./total no. (%)	1968/6014 (32.7)	1981/6076 (32.6)	1933/6022 (32.1)
Previous stroke or transient ischemic attack — no./total no. (%)	1195/6015 (19.9)	1233/6076 (20.3)	1195/6022 (19.8)
Prior myocardial infarction — no./total no. (%)	1008/6015 (16.8)	1029/6076 (16.9)	968/6022 (16.1)
Heart failure — no./total no. (%)	1937/6015 (32.2)	1934/6076 (31.8)	1922/6022 (31.9)
Diabetes mellitus — no./total no. (%)	1409/6015 (23.4)	1402/6076 (23.1)	1410/6022 (23.4)
Hypertension — no./total no. (%)	4738/6015 (78.8)	4795/6076 (78.9)	4750/6022 (78.9)

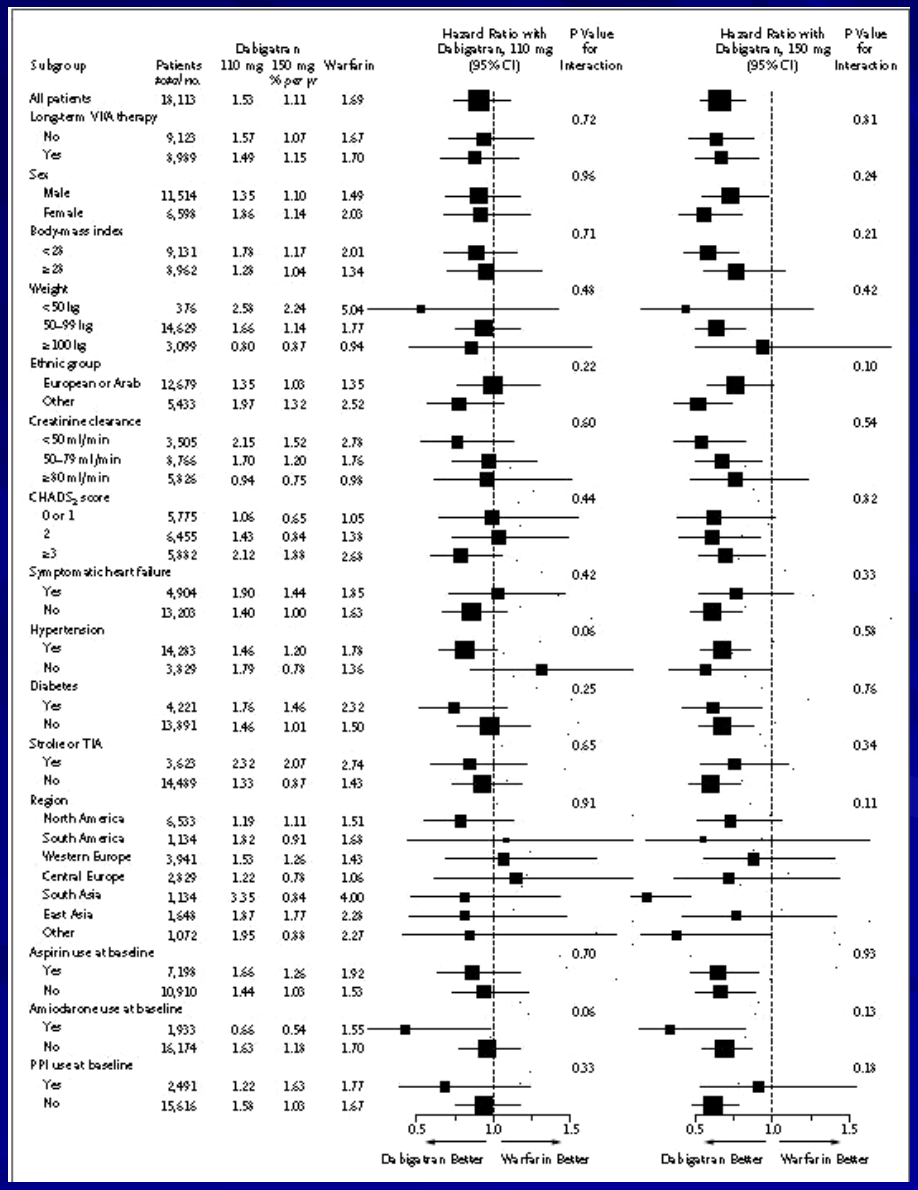
Re-ly Trial



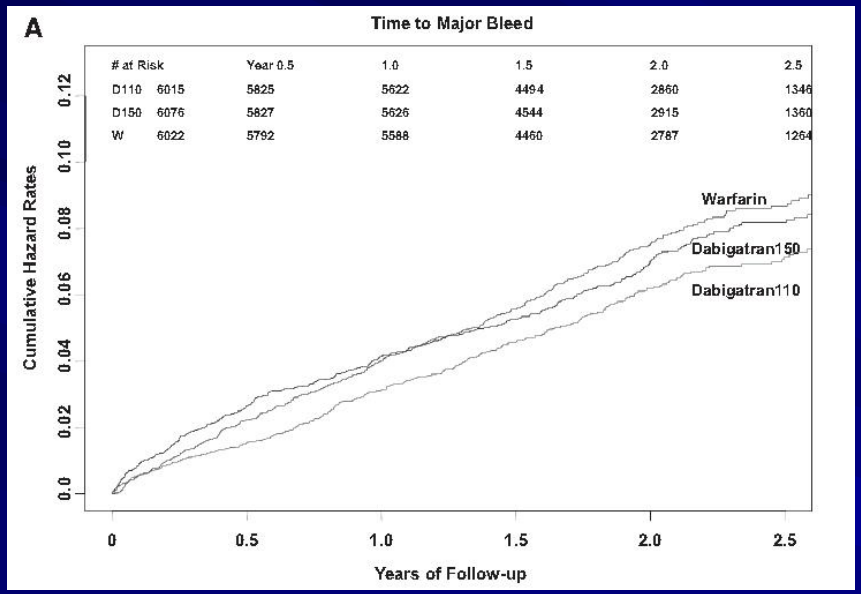
No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

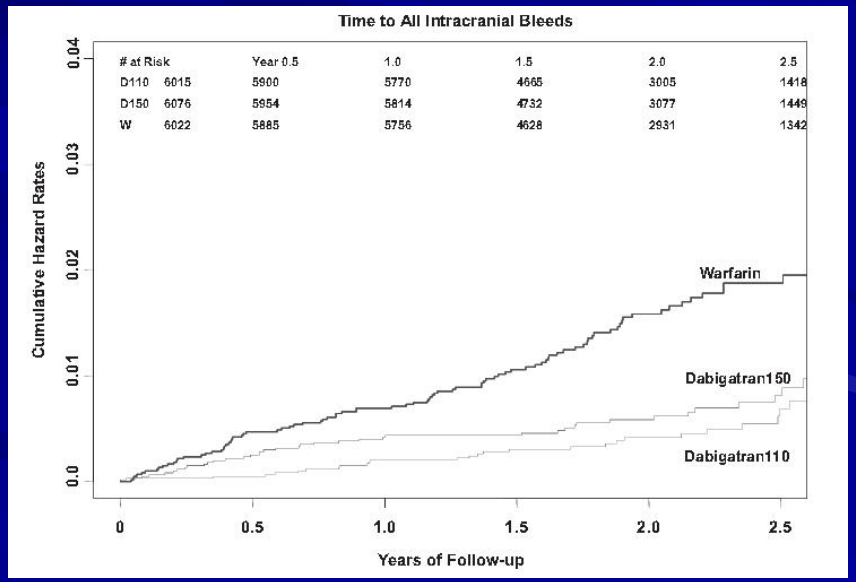
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Re-ly Trial


Subgroup
Patients total no.
Dabigatran 110 mg % per yr
Dabigatran 150 mg % per yr
Warfarin
Hazard Ratio with Dabigatran, 110 mg (95% CI)
P Value for Interaction
Hazard Ratio with Dabigatran, 150 mg (95% CI)
P Value for Interaction
All patients 18,113 1.53 1.11 1.69
Long-term VKA therapy 0.72 0.81
No 9,123 1.57 1.07 1.67
Yes 8,989 1.49 1.15 1.70
Sex 0.96 0.24
Male 11,514 1.35 1.10 1.49
Female 6,598 1.86 1.14 2.03
Body-mass index 0.71 0.21
<28 9,131 1.78 1.17 2.01
≥28 8,962 1.28 1.04 1.34
Weight 0.48 0.42
<50 kg 376 2.58 2.24 5.04
50–99 kg 14,629 1.66 1.14 1.77
≥100 kg 3,099 0.80 0.87 0.94
Ethnic group 0.22 0.10
European or Arab 12,679 1.35 1.03 1.35
Other 5,433 1.97 1.32 2.52
Creatinine clearance 0.60 0.54
<50 ml/min 3,505 2.15 1.52 2.78
50–79 ml/min 8,766 1.70 1.20 1.76
≥80 ml/min 5,826 0.94 0.75 0.98
CHADS2 score 0.44 0.82
0 or 1 5,775 1.06 0.65 1.05
2 6,455 1.43 0.84 1.38
≥3 5,882 2.12 1.38 2.68
Symptomatic heart failure 0.42 0.33
Yes 4,904 1.90 1.44 1.85
No 13,208 1.40 1.00 1.63
Hypertension 0.06 0.58
Yes 14,283 1.46 1.20 1.78
No 3,829 1.79 0.78 1.36
Diabetes 0.25 0.76
Yes 4,221 1.76 1.46 2.32
No 13,891 1.46 1.01 1.50
Stroke or TIA 0.65 0.34
Yes 3,623 2.32 2.07 2.74
No 14,489 1.33 0.87 1.43
Region 0.91 0.11
North America 6,533 1.19 1.11 1.51
South America 1,134 1.82 0.91 1.68
Western Europe 3,941 1.53 1.26 1.43
Central Europe 2,829 1.22 0.78 1.06
South Asia 1,134 3.35 0.84 4.00
East Asia 1,648 1.87 1.77 2.28
Other 1,072 1.95 0.88 2.27
Aspirin use at baseline 0.70 0.93
Yes 7,198 1.66 1.26 1.92
No 10,910 1.44 1.03 1.53
Amiodarone use at baseline 0.06 0.13
Yes 1,933 0.66 0.54 1.55
No 16,174 1.63 1.18 1.70
PPI use at baseline 0.33 0.18
Yes 2,491 1.22 1.63 1.77
No 15,616 1.58 1.03 1.67
0.5
1.0
1.5
Dabigatran Better
Warfarin Better
0.5
1.0
1.5
Dabigatran Better
Warfarin Better

Re-ly Bleeding risks





ARISTOTLE Trial

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

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Apixaban

- Direct acting (reversible) factor Xa inhibitor
- ½ half is ~12 hours
- Balanced elimination (~25% renal excretion)
- Good oral bioavailability
- Shown to be effective and safe for prevention of VTE after elective orthopedic surgery

ARISTOTLE Trial

- Randomized, double-blind trial comparing Apixaban 5mg BID to Warfarin (target INR 2-3)
- 18,201 patients from 1034 clinical sites and 39 countries
- Median duration of f/u was 1.8 years

Inclusion Criteria

- Had afib or flutter at enrollment OR 2 or more episodes of afib/flutter at least 2 weeks apart 12 months before enrollment
- ≥1 of the following risk factors for stroke:
  - At least 75 yrs of age
  - Previous stroke/TIA/systemic embolization
  - Symptomatic CHF within 3 months of enrollment or EF ≤40%
  - DM
  - HTN on Rx

Efficacy and Safety Outcomes

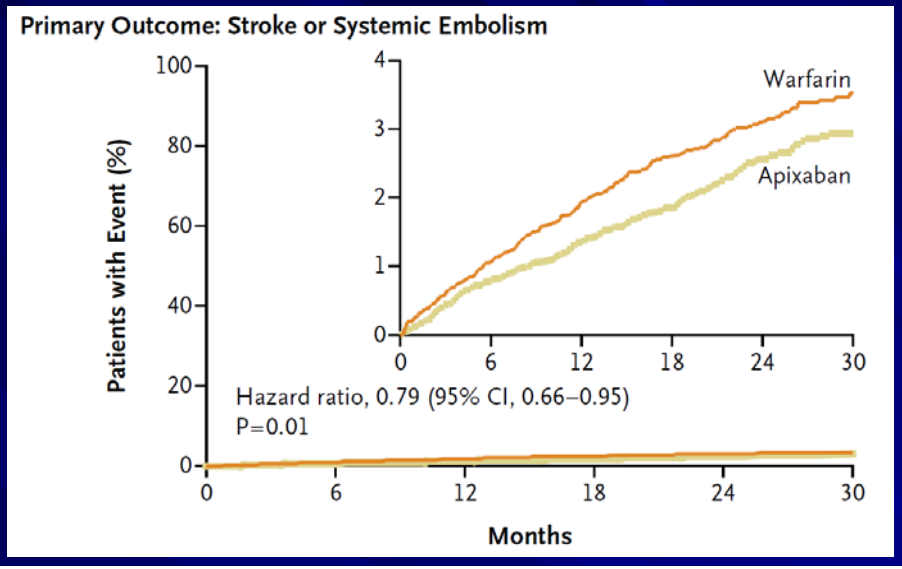
- Primary Efficacy Outcome: ischemic or hemorrhagic stroke or systemic embolization
- Secondary Efficacy Outcome: death from any cause, rate of MI

- Primary Safety Outcome: Major bleeding (leading to drop of Hgb>2 OR requiring 2u pRBCs and occurring at a critical site OR resulting in death)
- Secondary safety Outcome: Major bleeding and clinical relevant non-major bleeding (leading to hospitalization or change in Rx)

Baseline Characteristics

- Well balanced
- Median age was 70
- ~35% women
- Mean CHADS2 score was 2
- 57% were previously on warfarin
- ~19% had previous stroke/TIA or systemic embolism

Characteristic	Apixaban (N=9120)	Warfarin (N=9081)
Age — yr		
Median	70	70
Interquartile range	63–76	63–76
Female sex — no. (%)	3234 (35.5)	3182 (35.0)
Region — no. (%)		
North America	2249 (24.7)	2225 (24.5)
Latin America	1743 (19.1)	1725 (19.0)
Europe	3672 (40.3)	3671 (40.4)
Asian Pacific	1456 (16.0)	1460 (16.1)
Systolic blood pressure — mm Hg		
Median	130	130
Interquartile range	120–140	120–140
Weight — kg		
Median	82	82
Interquartile range	70–96	70–95
Prior myocardial infarction — no. (%)	1319 (14.5)	1266 (13.9)
Prior clinically relevant or spontaneous bleeding — no. (%)	1525 (16.7)	1515 (16.7)
History of fall within previous year — no. (%)	386 (4.2)	367 (4.0)
Type of atrial fibrillation — no. (%)		
Paroxysmal	1374 (15.1)	1412 (15.5)
Persistent or permanent	7744 (84.9)	7668 (84.4)
Prior use of vitamin K antagonist for >30 consecutive days — no. (%)	5208 (57.1)	5193 (57.2)
Qualifying risk factors		
Age ≥75 yr — no. (%)	2850 (31.2)	2828 (31.1)
Prior stroke, TIA, or systemic embolism — no. (%)	1748 (19.2)	1790 (19.7)
Heart failure or reduced left ventricular ejection fraction — no. (%)	3235 (35.5)	3216 (35.4)
Diabetes — no. (%)	2284 (25.0)	2263 (24.9)
Hypertension requiring treatment — no. (%)	7962 (87.3)	7954 (87.6)
$CHADS_2$ score		
Mean	2.1±1.1	2.1±1.1
Distribution — no. (%)		
1	3100 (34.0)	3083 (34.0)
2	3262 (35.8)	3254 (35.8)
≥3	2758 (30.2)	2744 (30.2)



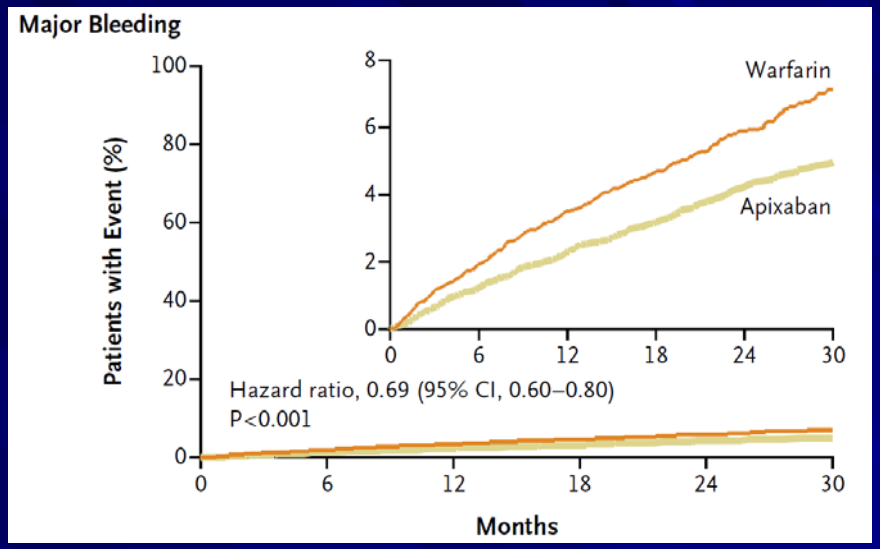
Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	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

Rate of Hemorrhagic stroke was 49% lower in the apixaban group

Rate of Ischemic or uncertain type of stroke was 8% lower in apixaban group

In pts with ischemic strokes, hemorrhagic conversion occurred in 12pts in the apixaban group vs. 20pts in the warfarin group

Fatal or disabling stroke occurred in 84pts (0.5%/yr) in the apixaban group vs 117pts (0.7%/yr) in the warfarin group…fatal strokes 42 vs 67pts (apixaban vs warfarin group, respectively)



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

7.7% absolute reduction in any bleeding in the apixaban group

ARISTOTLE Trial
Death rates

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

Apixaban Group

Warfarin Group

Death from CV causes (including from hemorrhagic stroke)

1.8%/yr

2.02%/yr (CI 0.76-1.04)

Death from Non-CV causes (including fatal bleeding except hem. stroke)

1.14%/yr

1.22%/yr (CI 0.77-1.33)

Conclusions

- Apixaban was not only non-inferior, but superior, to warfarin in preventing stroke or systemic embolization
- Apixaban had a better bleeding profile vs warfarin
- Apixaban also showed a significant reduction in death from any cause vs warfarin

Conclusions

- Direct thrombin inhibitors useful for:
  - HIT
  - Pts with history of HIT needing IV AC
  - Prevention of Venous Thromboembolism after orthopedic surgery
  - Atrial fibrillation in appropriate patients

Future Directions & Concerns

- Cost- effectiveness (drug cost vs health care system costs)
- Though risks of bleeding are lower, drugs to reverse effects are still under investigation and not readily available
- No current indications with valvular heart disease and prosthetic heart valves