Atrial Fibrillation, Stroke, and Anticoagulation

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BAPTIST HEARTWISE

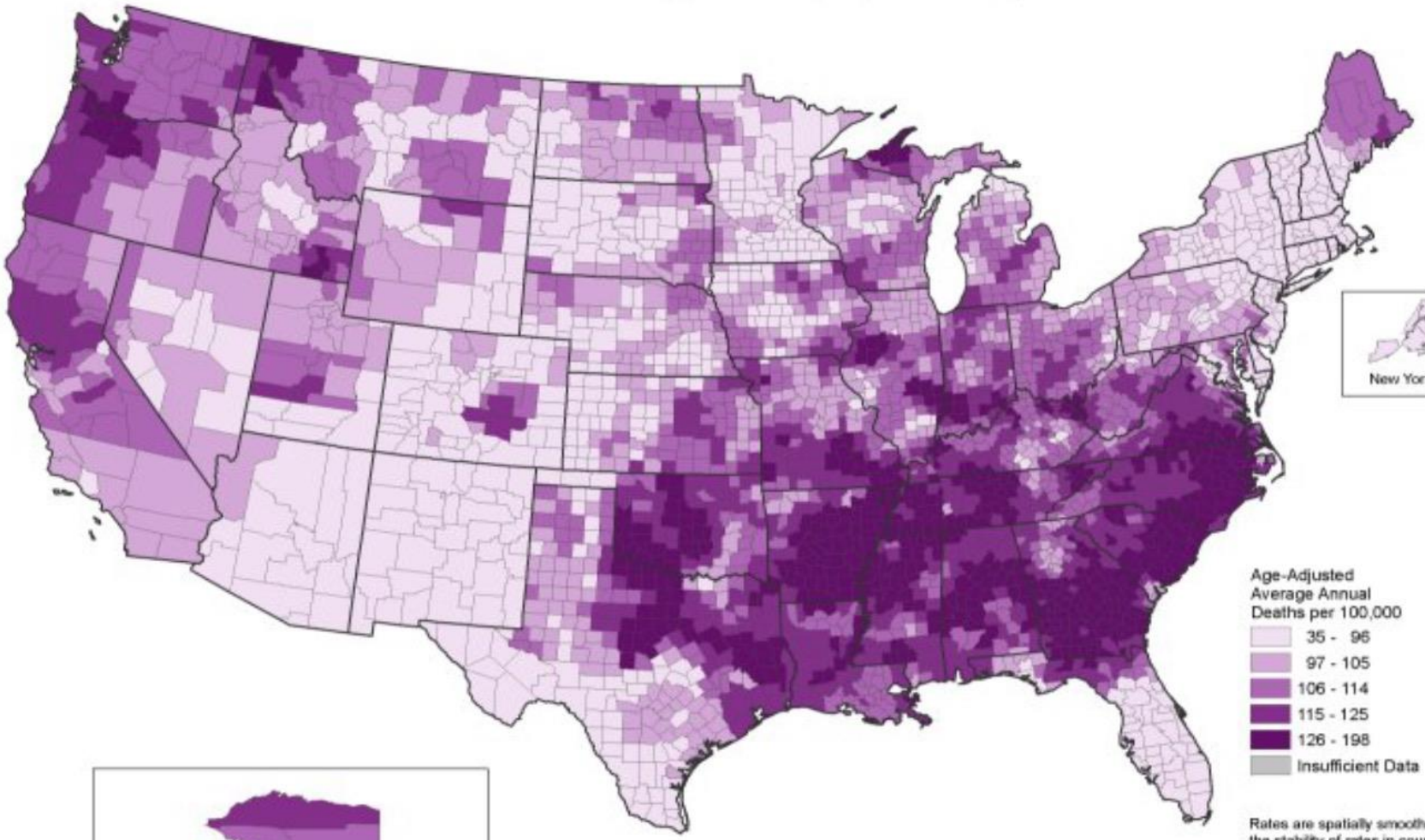
Disclosure

- Speaker for GILEAD

OUTCOME: STROKE

- 130,000 AMERICANS DIE FROM STROKE EACH YEAR, 1 of every 19 deaths
- IN THE US, SOMEONE HAS A STROKE EVERY 40 SECONDS
- EVERY YEAR ABOUT 795,000 PEOPLE IN THE US HAVE A STROKE, AND IS A MAJOR CAUSE OF DISABILITY
- STROKE COST THE NATION $38.6 BILLION ANNUALLY (HEALTHCARE COST, MEDICATIONS, LOST PRODUCTIVITY)

Stroke Death Rates, 2000-2006
Adults Ages 35+, by County



Age-Adjusted Average Annual Deaths per 100,000	Number of Counties
35 - 96	679
97 - 105	624
106 - 114	676
115 - 125	615
126 - 198	544
Insufficient Data	3

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

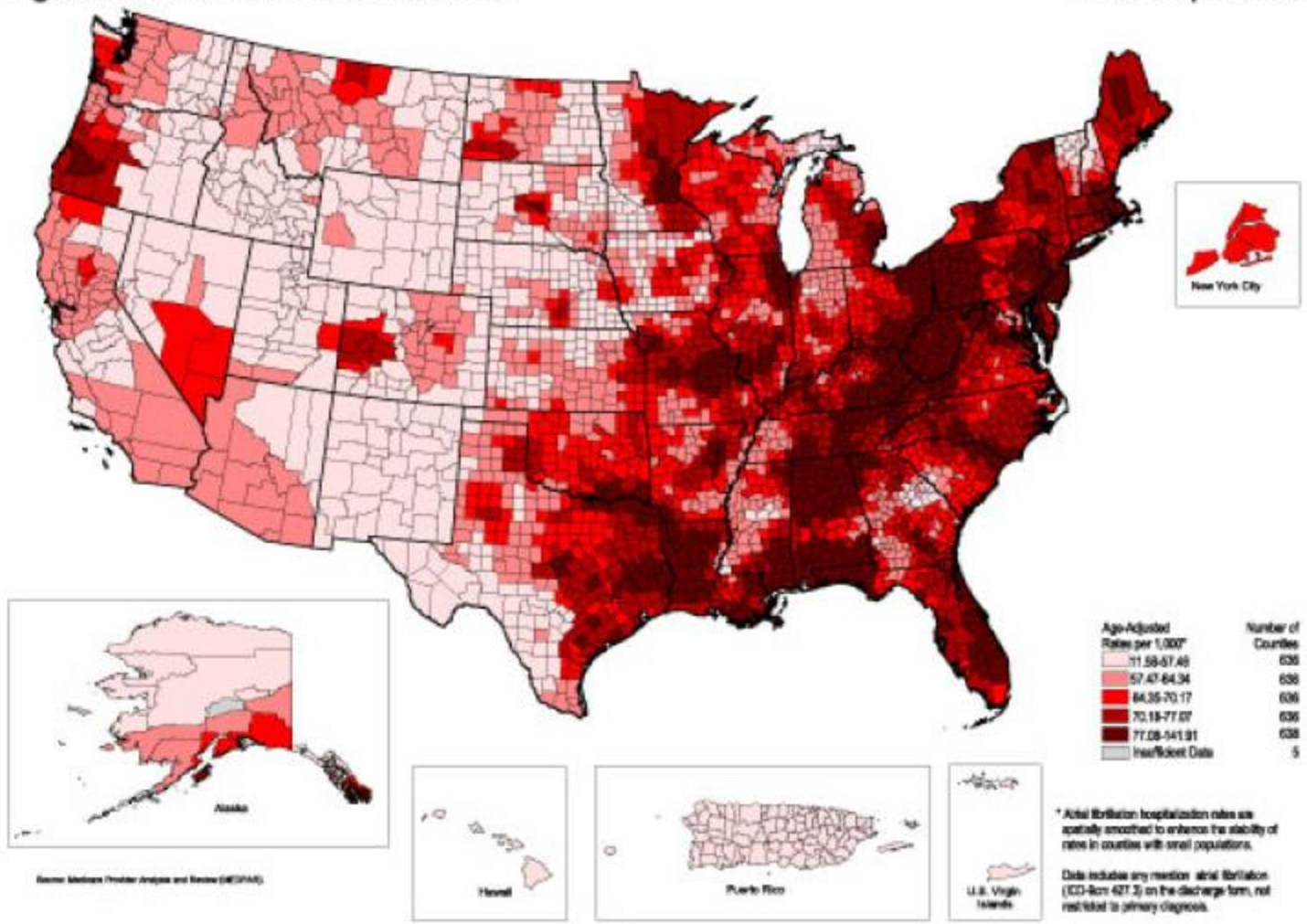
ICD-10 codes for stroke: I60-I69

Data Source: National Vital Statistics System and the U.S. Census Bureau

ATRIAL FIBRILLATION

- 3 million people are diagnosed with afib
- Projected to increases to 12 million patients in 30 years
- 70% of afib patients 65-85 years old
- In 2005 cost $6.5 billion in hospital costs
- **15-20% of ischemic strokes due to afib**
- 80,000 people die a year from afib and its complications

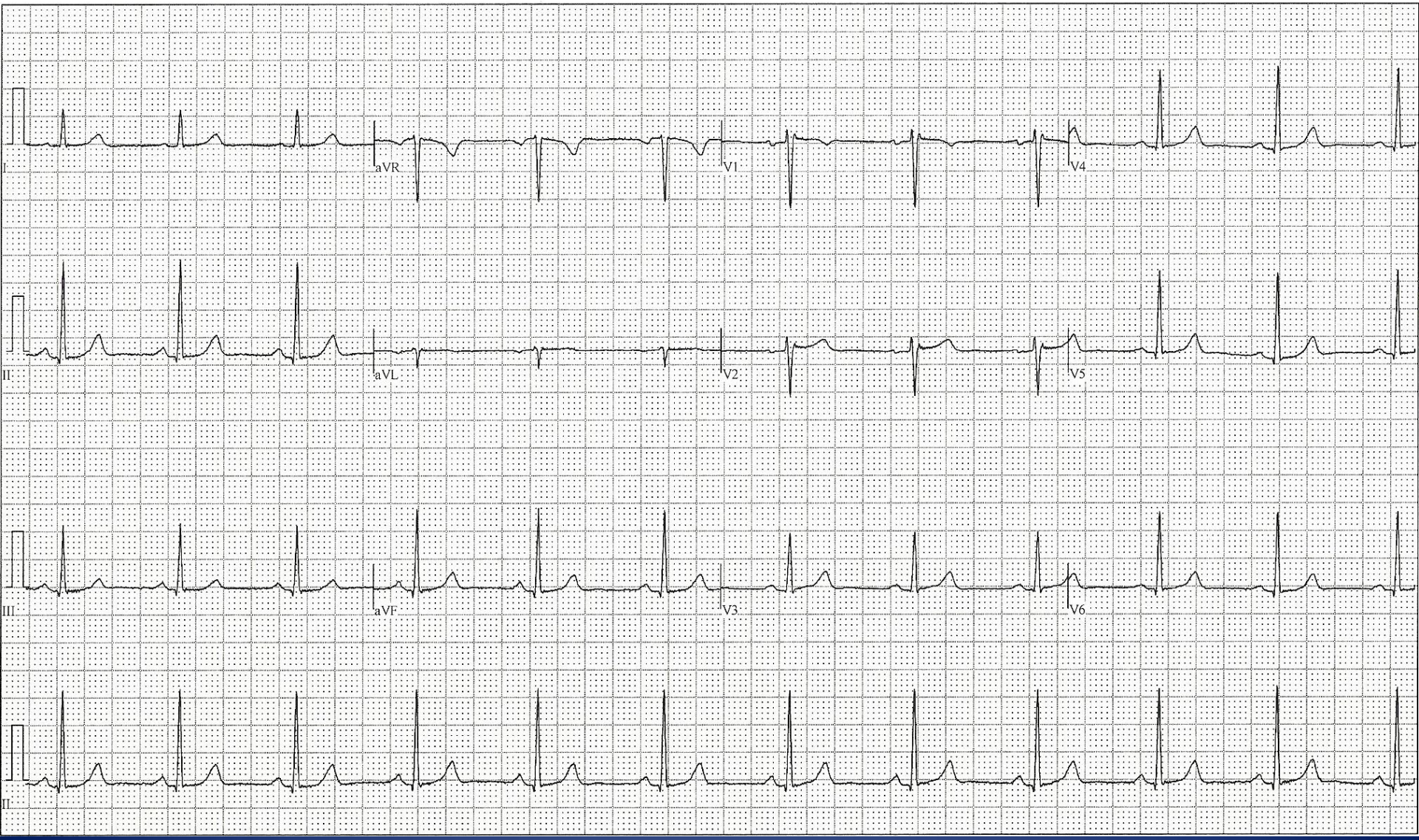
Atrial Fibrillation Fact Sheet



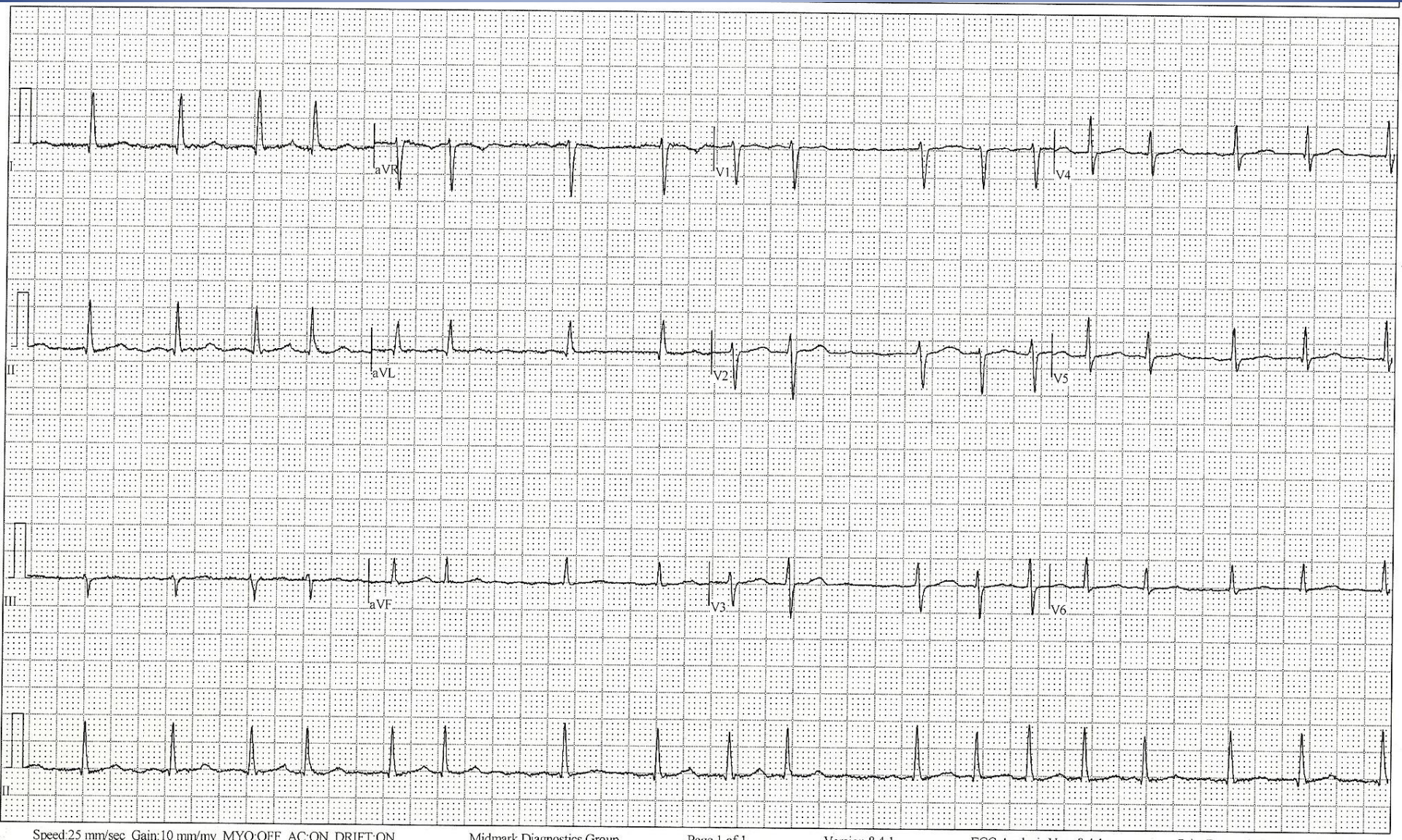
DEFINITION OF AF

TERM	DEFINITION
PAROXYSMAL AF	AF THAT TERMINATES SPONTANEOUSLY OR WITH INTERVENTION WITHIN 7 DAYS OF ONSET
PERSISTENT AF	CONTINUOUS AF >7DAYS
PERMANENT AF	PATIENT AND CLINICIAN MAKE A JOINT DECISION TO STOP FURTHER ATTEMPTS TO RESTORE AND OR MAINTAIN SINUS RHYTHM
NONVALVULAR AF	AF IN THE ABSENCE OF MITRAL STENOSIS, MECHANICAL OR BIOPROSTHETIC HEART VALVE OR MITRAL VALVE REPAIR

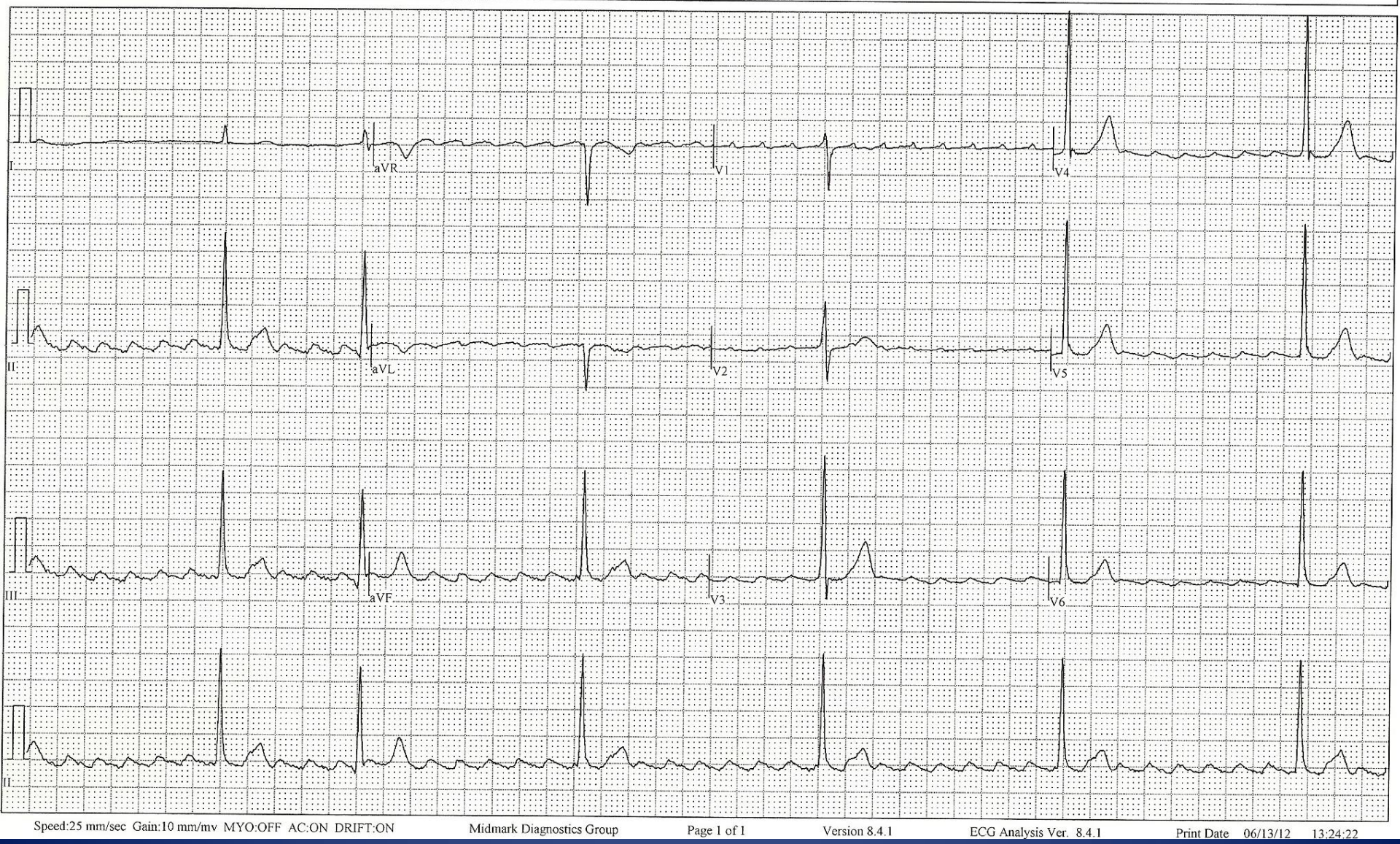
Sinus Rhythm



Atrial Fibrillation

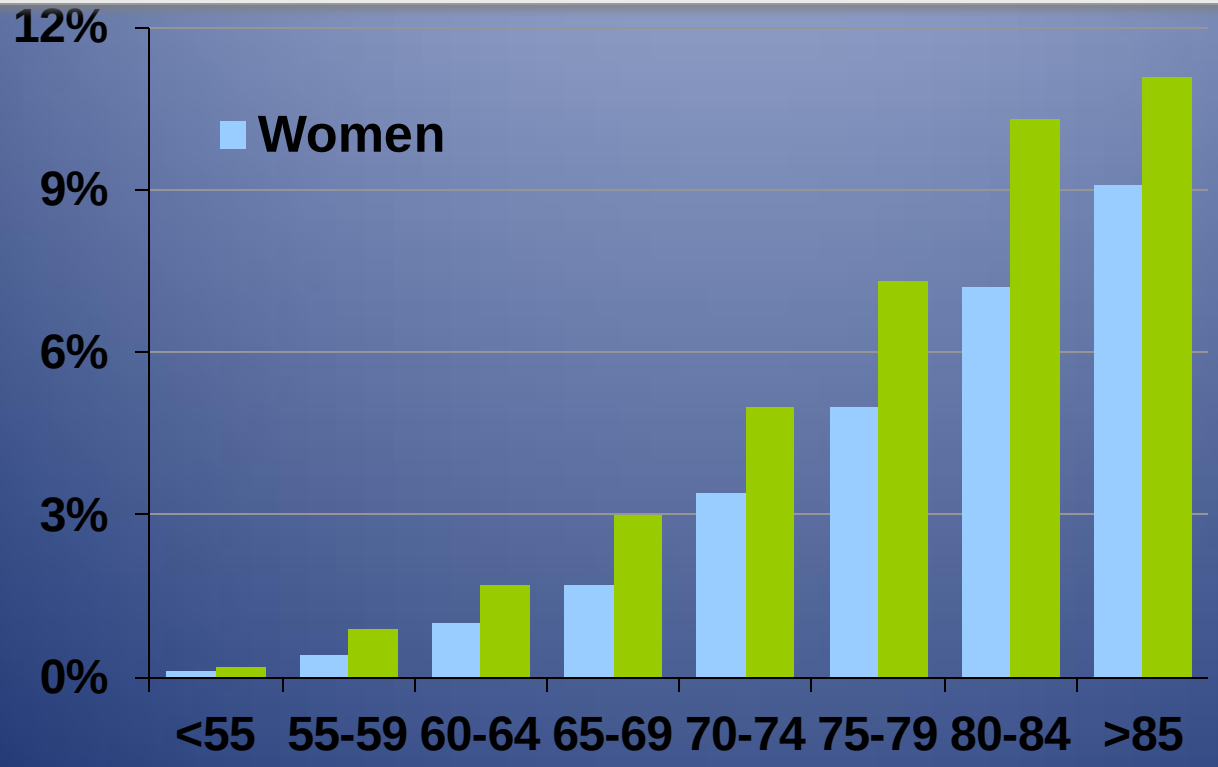


Atrial Flutter



AF
Prevalence Stratified by Age and Sex[1]

The lifetime risk of developing AF after age 40 is 1 in 4[2]



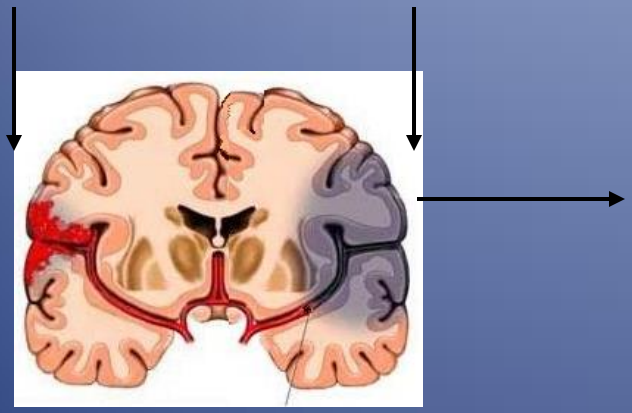
1. Go A. et al. Prevalence of Diagnosed Atrial Fibrillation in Adults National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation Factors In Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285:2370-2375.
2. Lloyd-Jones D. et al. Lifetime Risk for Development of Atrial Fibrillation: The Framingham Heart Study. Circulation. 2004;110:1042-1046.

Stroke Etiologies

The Challenge of Cryptogenic Stroke

Vessel Rupture (15%)

Artery Occlusion (85%)



Types of Ischemic Stroke

Atherothrombotic (25-30%)

Stenotic artery feeding area of infarction

Cardioembolic (20%)

A thrombus or other material dislodges from the heart or aortic arch

Other/Uncommon (5-10%)

Cryptogenic (25-40%)

Unknown cause

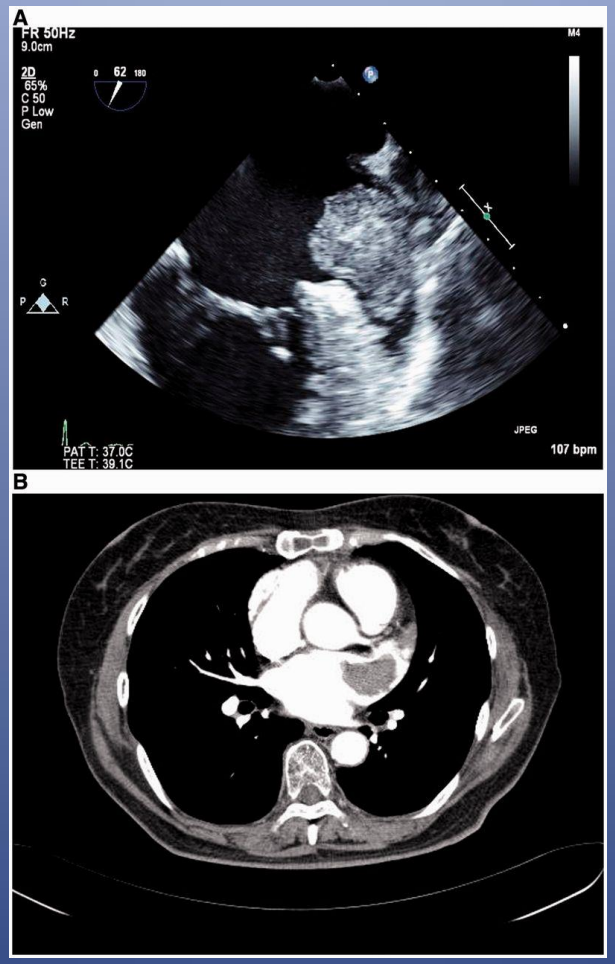
Adams HP Jr, *Classification of Subtype of Acute Ischemic Stroke*. Stroke. Jan 1993; 24; 35-41

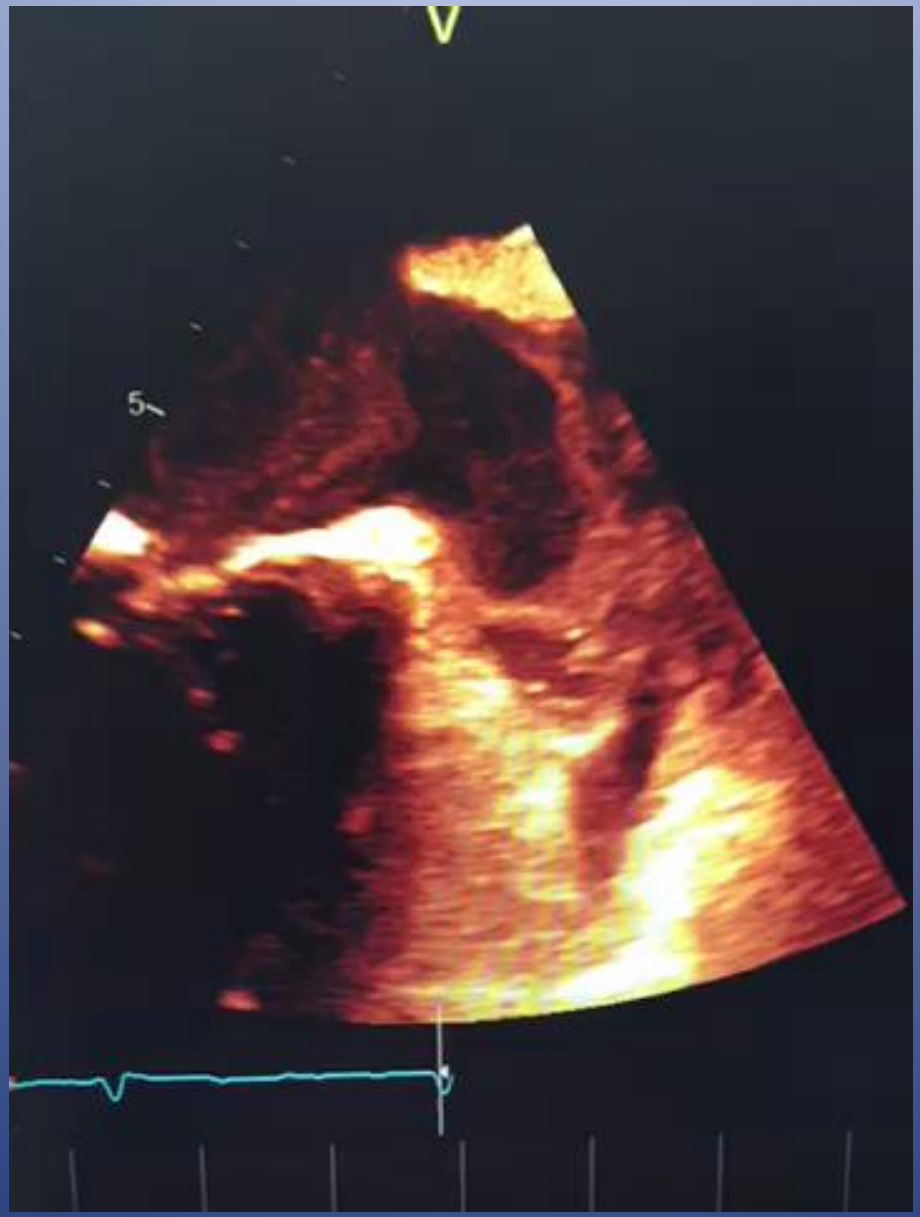
Cryptogenic Stroke
Why AF Matters

- AF equals 5 fold increase for stroke risk[1]
- Up to 90% of Paroxysmal Atrial Fibrillation (PAF) episodes may be asymptomatic.[2]
- Risk of stroke annually is equal for PAF and permanent AF [3]
- Detection of AF in Cryptogenic Stroke Patients changes treatment
  - Guidelines state change from antiplatelet to OAC[4]

1. Wolf PA, et al. *Stroke* 1991;22:983-988 ;
2. Isreal et al, J AM Coll Cardiol. 2004;43:47-52;
3. Page, RL, et al Circulation. 1994;89:224-227 Hart RG, et al Coll Cardiol. 2000; 35:183-187
4. Camm et al, European Heart Journal . 2012; 33, 2719-2747

IMAGE OF LAA THROMBUS

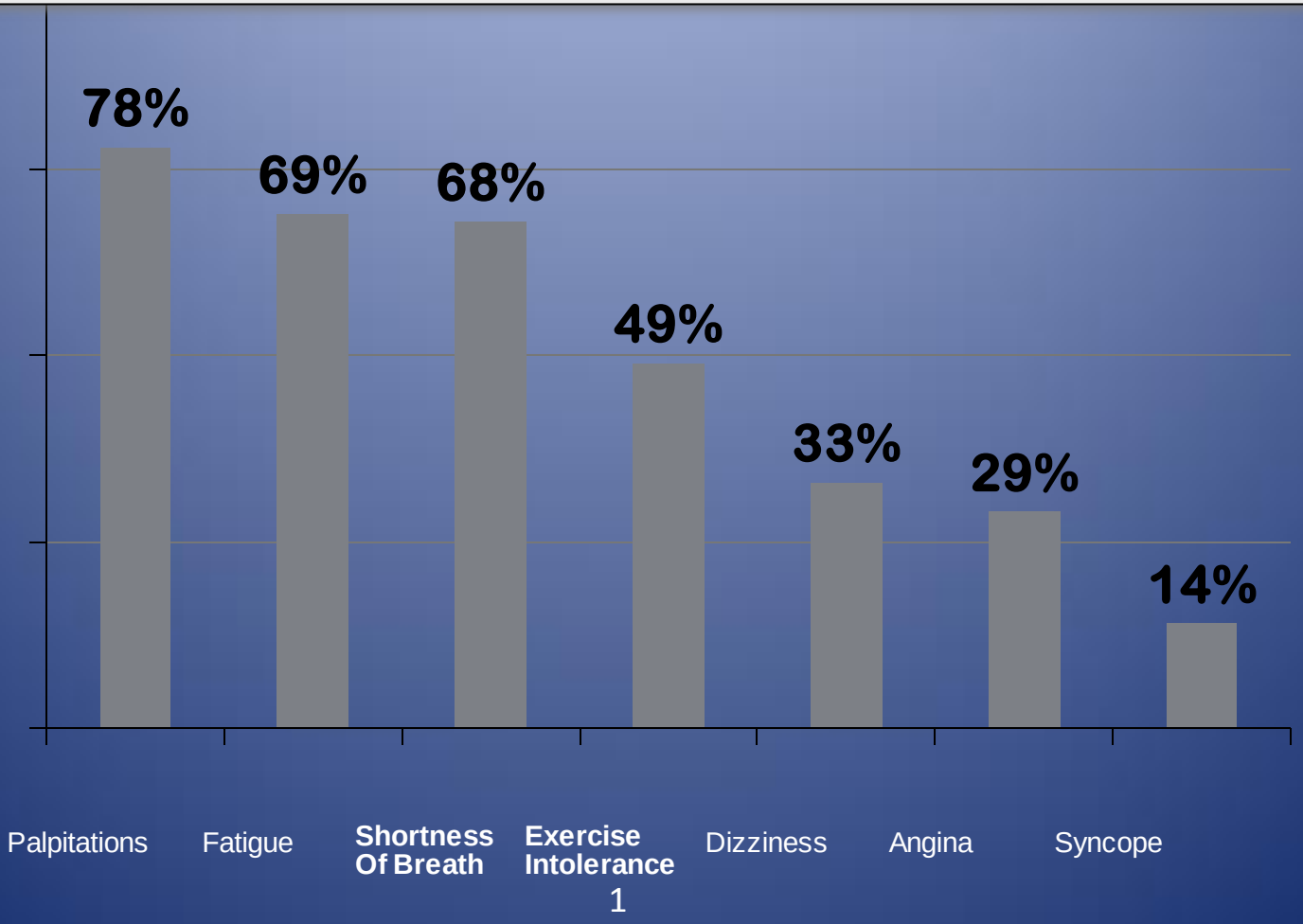



V
5

AF

Symptoms

Select Symptoms from 147 Patients During AF[1]



1

1. Luderitz B. et al. Quality of Life in Atrial Fibrillation. Journal of Interventional Cardiac

AF Discovery / Monitoring

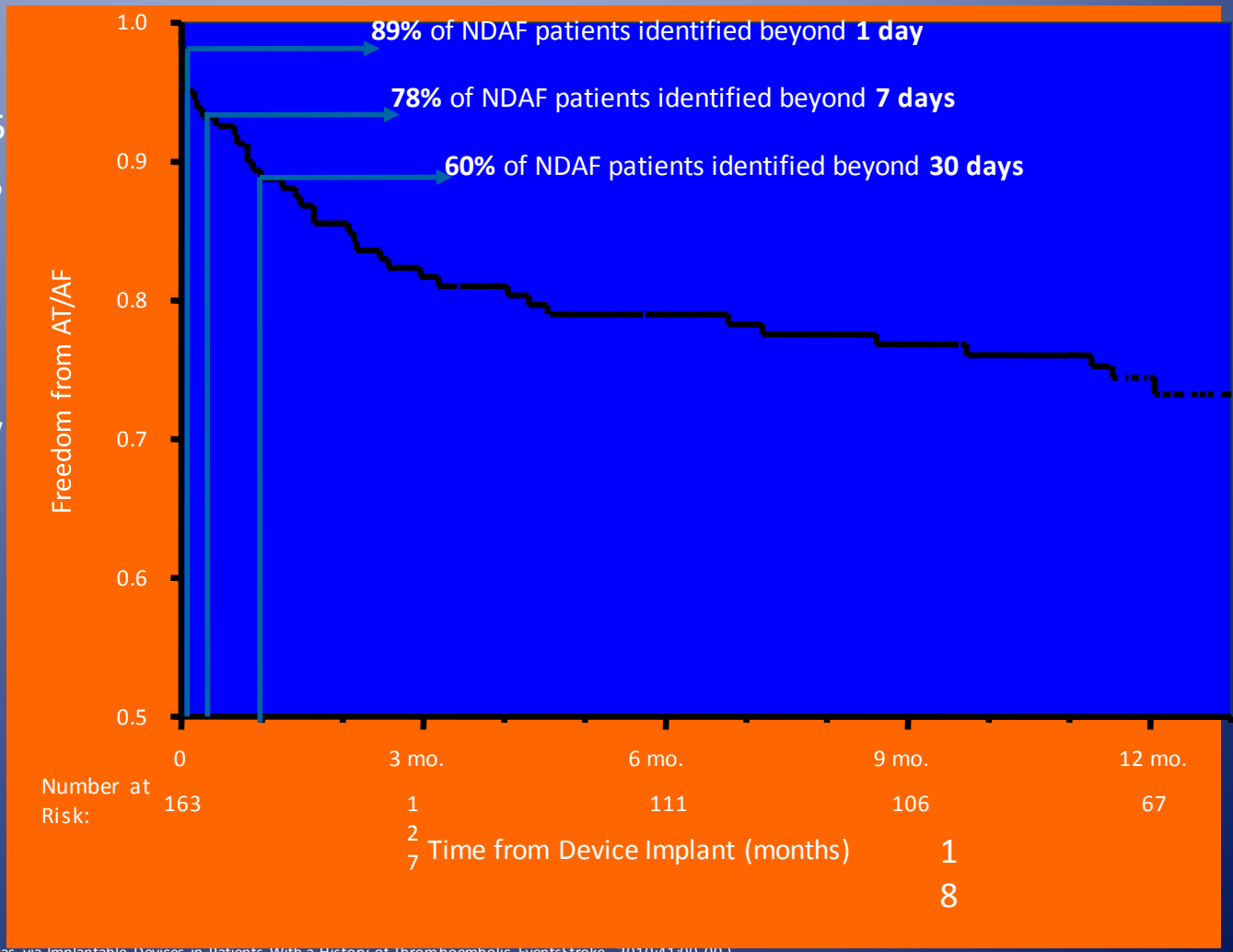
- Symptoms are not a reliable indicator of AT/AF.
  - 90% of AF episodes are asymptomatic[1]
  - 20% of reported symptoms are due to AF[1]
- External monitors (Holter monitors or event recorders)
  - Low yield due to poor compliance
  - Intermittent sampling[2]
- Implantable systems (e.g. Pacemaker/ICD)
  - Sensitivity of 100% and PPV of 95%[3]
  - Can only be used in indicated patients

[1] Strickberger et al. *Heart Rhythm.* 2005;2:125-31
[2] Ziegler et al. *Heart Rhythm*. 2006;3:1445-1452
[3] Puererfellner et al. *Pacing Clin Electrophysiol*. 2004;27:983-92

TRENDS Study Subgroup Analysis[1]

Newly Detected AF ("NDAF") in Patients with Thromboembolic Events

- Of 163 patients with previous ischemic stroke/TIA, no known AF, and continuous monitoring via pacemaker or ICD, NDAF ≥ 5 minute duration was found in 45 patients (28%).
- **"The majority of NDAF patients (73%) had AT/AF on <10% of follow-up days, making it highly unlikely to be detected by standard monitoring techniques."**



1. Ziegler P. et al. Incidence of Newly Detected Atrial Arrhythmias via Implantable Devices in Patients With a History of Thromboembolic EventsStroke. 2010;41:00-00.)

Glotzer: TRENDS Study[1]

Topic: Relationship Between Atrial Arrhythmia Burden and Stroke Risk

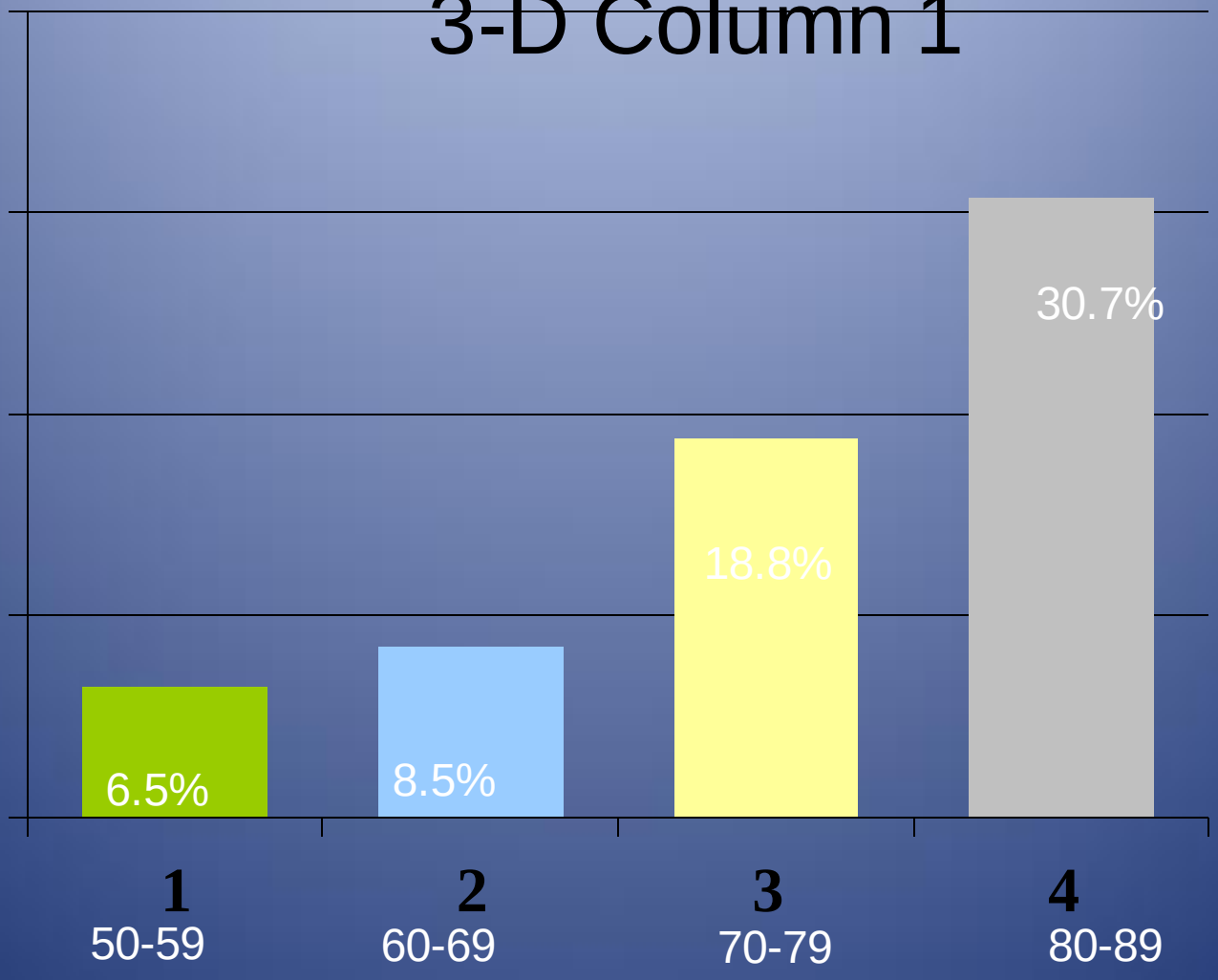
- Prospective, observational study analyzing 2,486 patients with ≥1 stroke risk receiving pacemakers or defibrillators that monitor AT/AF burden
- **AT/AF burden >5.5 hours on any of 30 prior days appeared to double thromboembolic (TE) risk**

AT/AF Burden Subset	Annualized TE Rate (95% Confidence Interval)
Zero AT/AF burden	1.1 [0.8, 1.6] %
Low AT/AF burden (<5.5 hours)	1.1 [0.4, 2.8] %
High AT/AF burden (≥5.5 hours)	2.4 [1.2, 4.5] %

1. Glotzer T. et al. The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and StrokeRisk The TRENDS Study Circ Arrhythmia Electrophysiol. 2009.

AF

Prevalence of AF in Stroke Cases by Age[1]



1.Wolf B. et al. *Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study*. Stroke 1991; 22:983-988.

CHADS Score

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHADS2 score	Patients (*n* = 1733)	Adjusted stroke rate %/year
0	120	1.9
1	463	2.8
2	**523**	**4.0**
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

CHA_2DS_2VASc Score

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

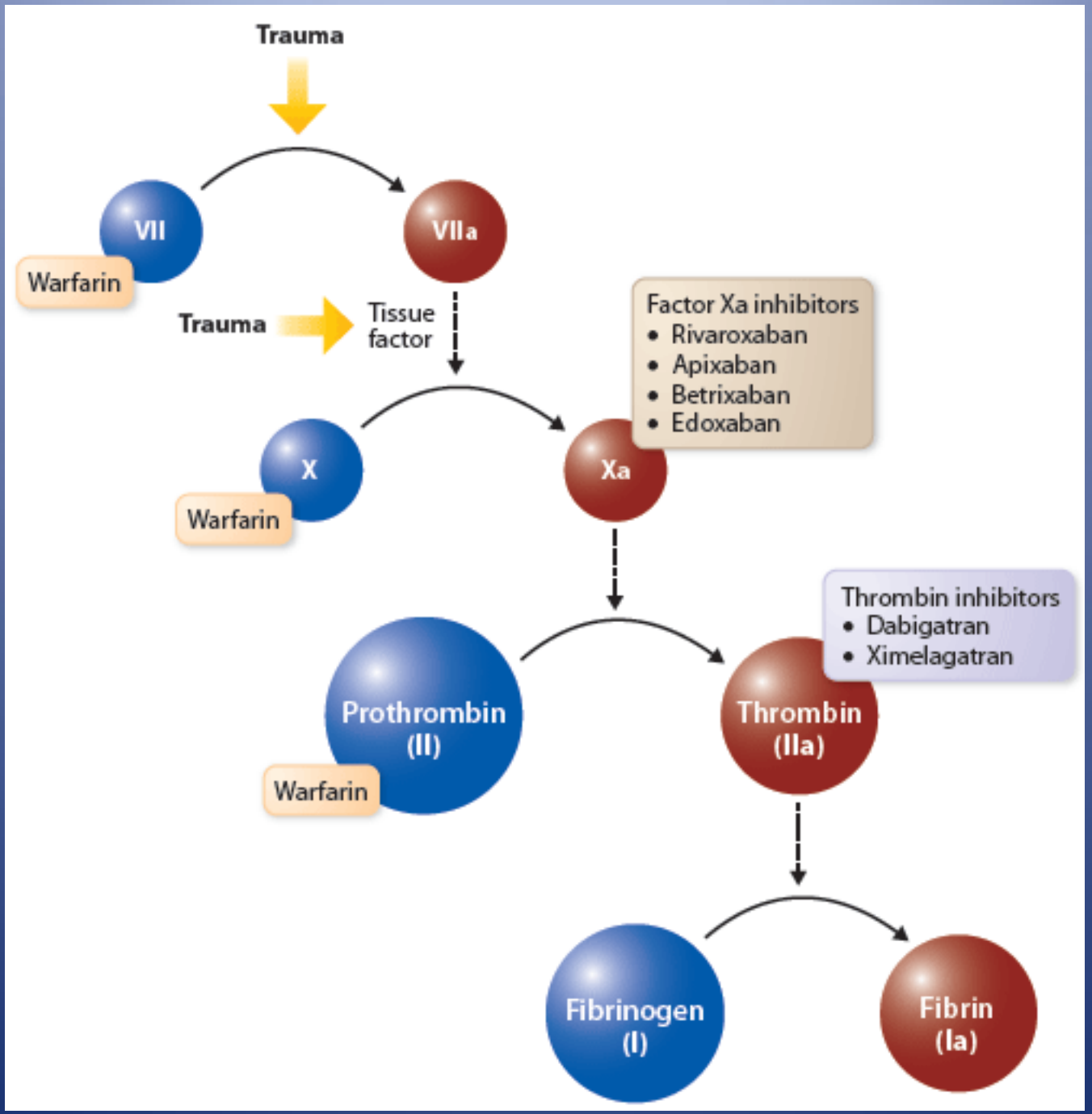
CHA2DS2-VASc score	Patients (*n* = 7329)	Adjusted stroke rate (%/year)
0	1	0
1	422	1.3
2	1230	2.2
3	**1730**	**3.2**
4	**1718**	**4.0**
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

Warfarin

- Old stand by for stroke Prevention in Afib
- Reduces stroke in afib by 64%
- Higher rates of intracranial and other hemorrhage
- Issues with compliance, diet limits, drug interaction

(Not so) New Kids On the block

- All are indicated for stroke prevent in AF that is NON-VALVULAR
- All four drugs do not require INR monitoring
- All four drugs have no diet restrictions
- All four drugs have renal dosing for CrC l < 30
- Formerly known as NOAC, now known as DOAC (Direct Oral AntiCoagulants)


Trauma
VII
Warfarin
VIIa
Trauma
Tissue factor
Factor Xa inhibitors
• Rivaroxaban
• Apixaban
• Betrixaban
• Edoxaban
X
Warfarin
Xa
Thrombin inhibitors
• Dabigatran
• Ximelagatran
Prothrombin (II)
Warfarin
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)

Dabigatran -Pradaxa

Dabigatran -Pradaxa

- Pro drug converted via serum esterase to active drug
- Direct Thrombin inhibitor
- 80% renal elimination
- Half life is 12-17 hours
- Fully anticoagulated in most patients within 90 minutes
- PTT can be 1.5 – 2.0x of lab control
- Thrombin time can be used

RELY - Dabigatran

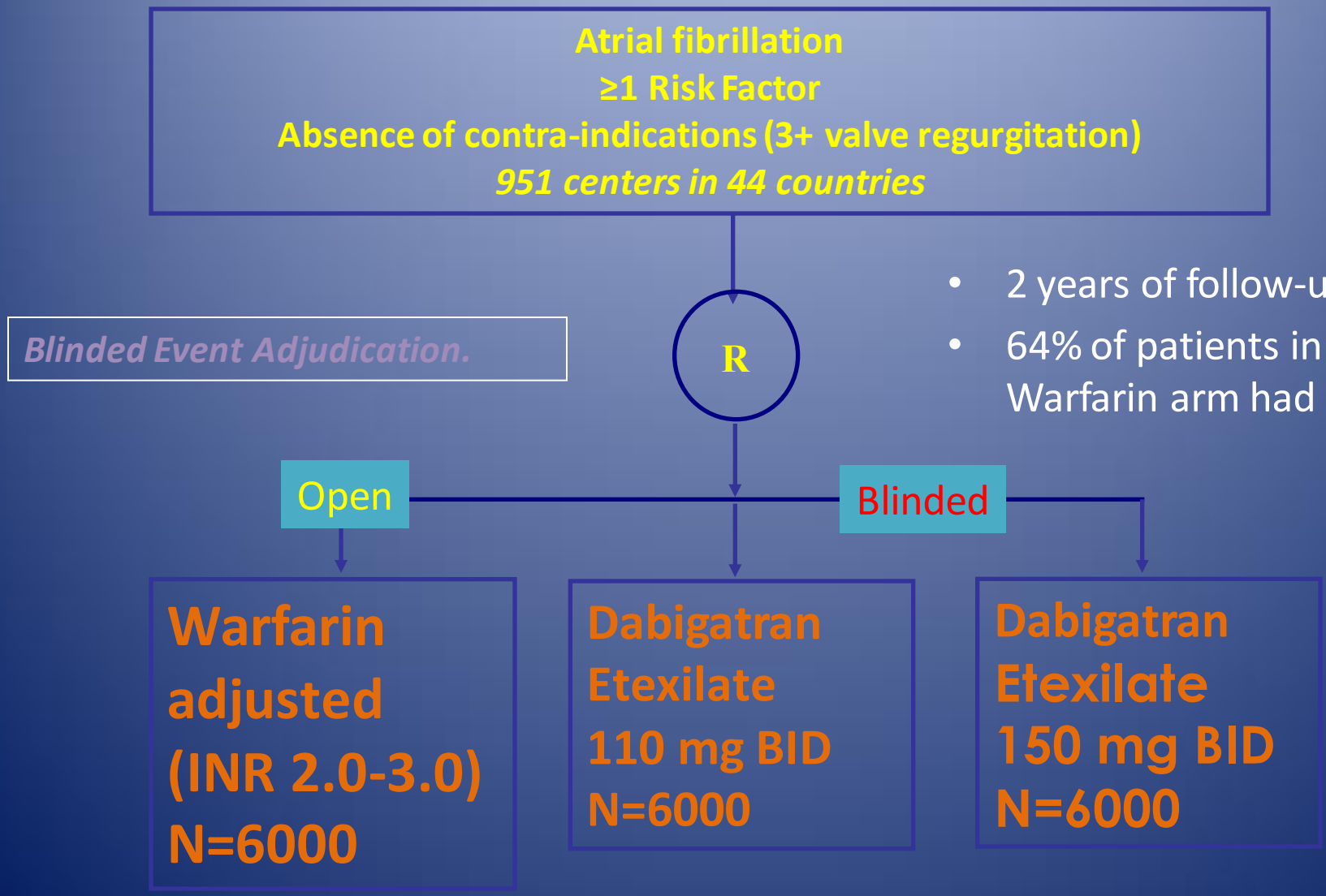
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RELY: A Non-inferiority Trial

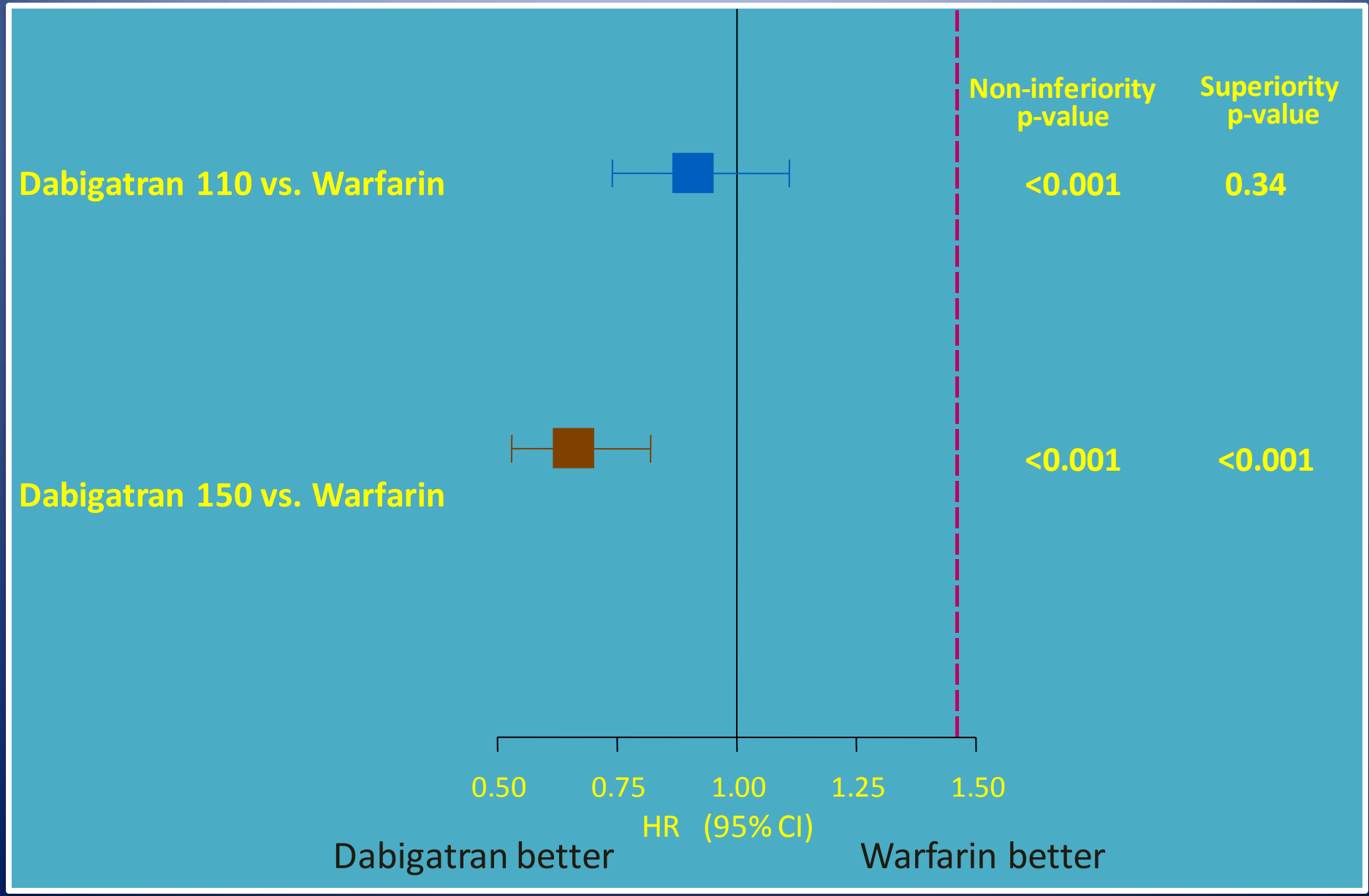


- 2 years of follow-up
- 64% of patients in the Warfarin arm had INRs 2-3

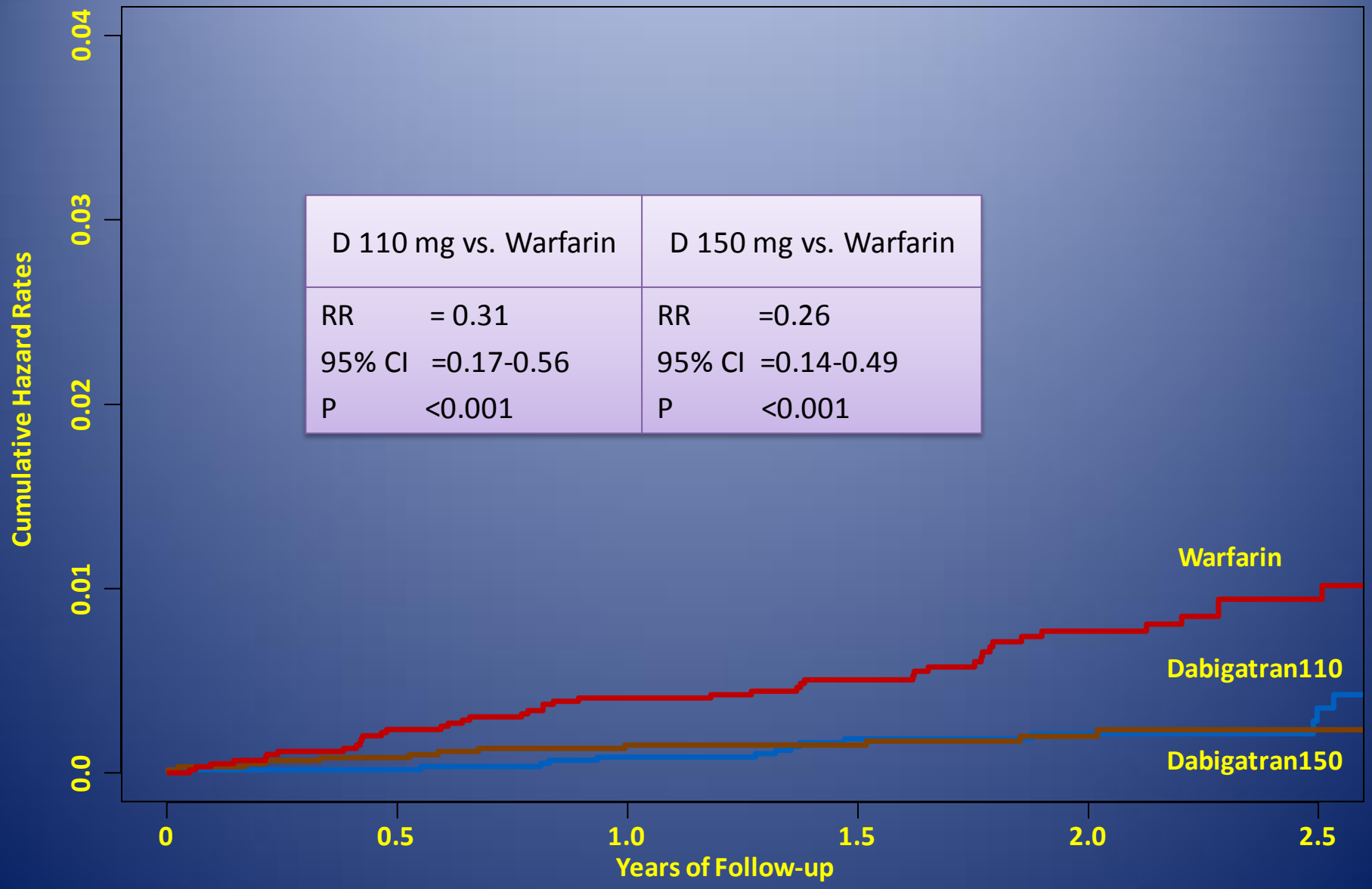
Baseline Characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

RELY -Stroke or Systemic Embolism



RELY - Hemorrhagic Stroke



D 110 mg vs. Warfarin	D 150 mg vs. Warfarin
RR = 0.31	RR =0.26
95% CI =0.17-0.56	95% CI =0.14-0.49
P <0.001	P <0.001

RELY – Dabigatran Conclusions

- The 150mg Dose significantly reduced stroke compared to warfarin with similar bleeding risks
- The 110mg dose (NOT in US), had equal stroke rates as warfarin with LESS major bleeding
- Both doses MARKEDLY reduced intra-cerebral, life threatening, and total bleeding
- Dyspepsia major side effect

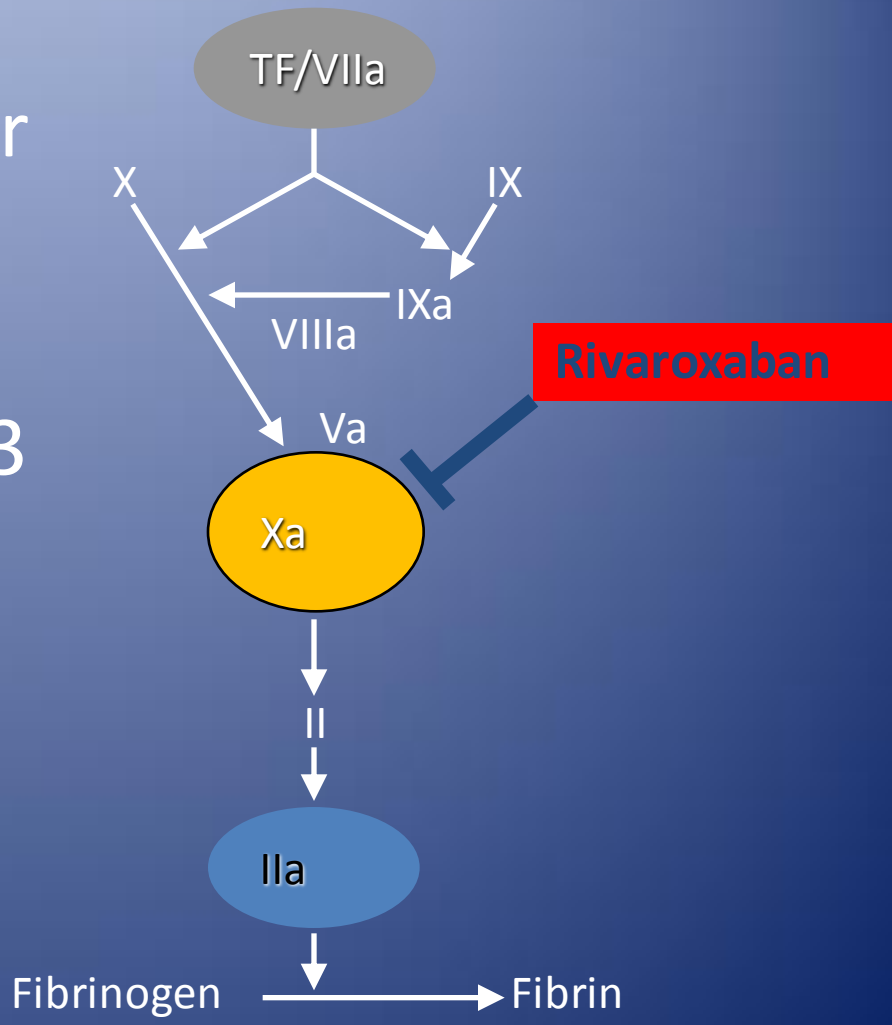
Dabigatran

- Approved by the FDA October 19, 2010
- Only approved the 150mg and 75mg dose based on superiority to warfarin, despite bleeding risk
- For renal patients with GFR less than 30, reduce the dose to 75mg BID
- If drug is in a bottle, only good for 1 month due to exposure to humidity. Blister packs are ok
- 30 days of 150mg dose BID is $245

Rivaroxaban (Xarelto)

Rivaroxaban

- Direct Factor Xa inhibitor
- Good gut absorption
- Full anticoagulation in about 4 hrs, half life 5-13 hrs
- 1/3 renal excretion, 2/3 CPY450 liver enzyme
- Lasts over 24hrs so once a day dosing is ok



Rocket AF - Rivaroxaban

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Study Design

Atrial Fibrillation

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind / Double Dummy
(n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

INR goal was 57.8% of warfarin patients

Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

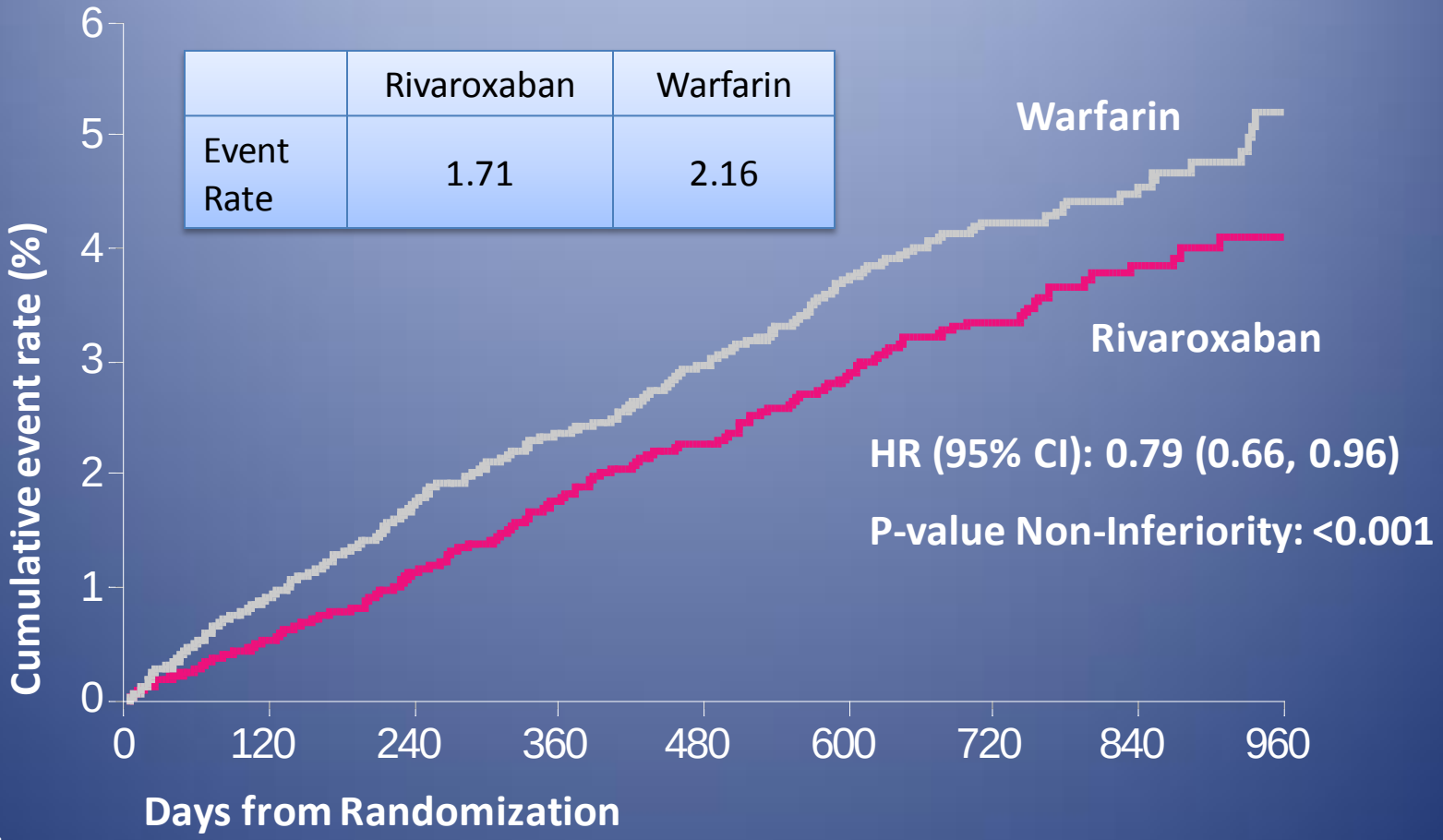
Baseline Demographics

	Rivaroxaban (N=7081)	Warfarin (N=7090)
$CHADS_2$ Score (mean)	3.48	3.46
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2
Prior VKA Use (%)	62	63
Congestive Heart Failure (%)	63	62
Hypertension (%)	90	91
Diabetes Mellitus (%)	40	39
Prior Stroke/TIA/Embolism (%)	55	55
Prior Myocardial Infarction (%)	17	18

Based on Intention-to-Treat Population

Rocket-AF: Primary Efficacy Outcome

Stroke and non-CNS Embolism



	Rivaroxaban	Warfarin
Event Rate	1.71	2.16

No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years

Based on Protocol Compliant on Treatment Population

Rocket AF : Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

Rocket AF Conclusions

- Rivaroxaban non inferior to warfarin on an intent-to-treat analysis
- Analyzed patients who received at least one dosage of the drug who were followed for events during treatment, Rivaroxaban was superior to warfarin
- No different than warfarin in bleeding rates
- Less intracranial and fatal bleeding with rivaroxaban
- Drug needs to be taken with food

Rivaroxaban - Xarelto

- Drug approved for DVT prophylaxis in knee and hip patients by FDA on July 1, 2011
- FDA approval on Nov 1, 2011 for stroke prevention in AF
- Approved for treatment in active DVT and PE

Rivaroxaban - Xarelto

- Dosed as 20mg a day at night
- Reduced to 15mg a day for GFR < 30
- 30 day cost about $220
- Take in the evening with food

Apixaban (Eliquis)

Apixaban

- Direct Factor Xa inhibitor
- Absorbed in Gut
- 50% Bioavailable
- Half life 6 hours
- Metabolized by liver CYP450
- 27% excretion in urine, rest in stool
- 5mg Bid
- 2.5mg BID if have 2 of following: over 80, less than 60kg, or Creatinine > 1.5

ARISTOTLE - Apixaban

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

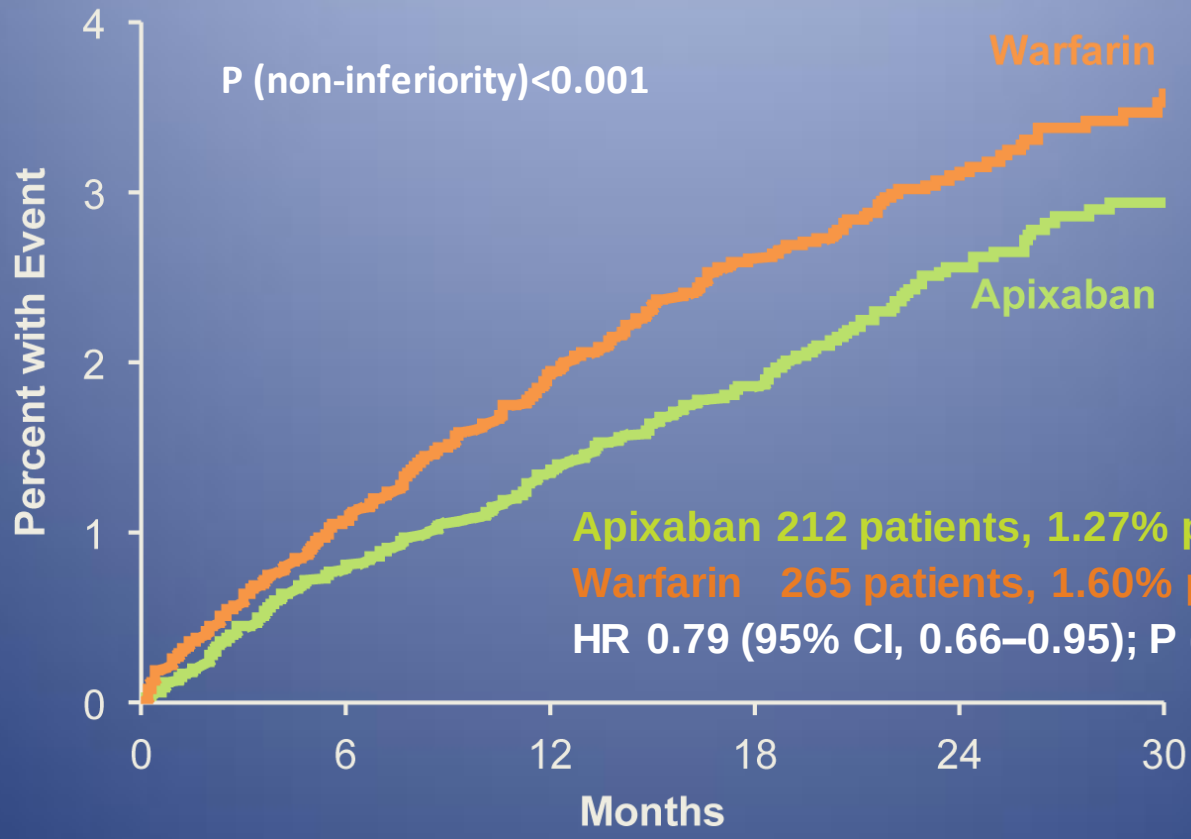
Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

ARISTOLE - Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (25th, 75th %ile)	70 (63, 76)	70 (63, 76)
Women, %	35	35
Region, %		
North America	25	25
Latin America	19	19
Europe	40	40
Asia/Pacific	16	16
Warfarin naïve, %	43	43
CHADS score, mean (+/- SD)	2.1 (+/- 1.1)	2.1 (+/- 1.1)
1, %	34	34
2, %	36	36
≥ 3, %	30	30

ARISTOLE - Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



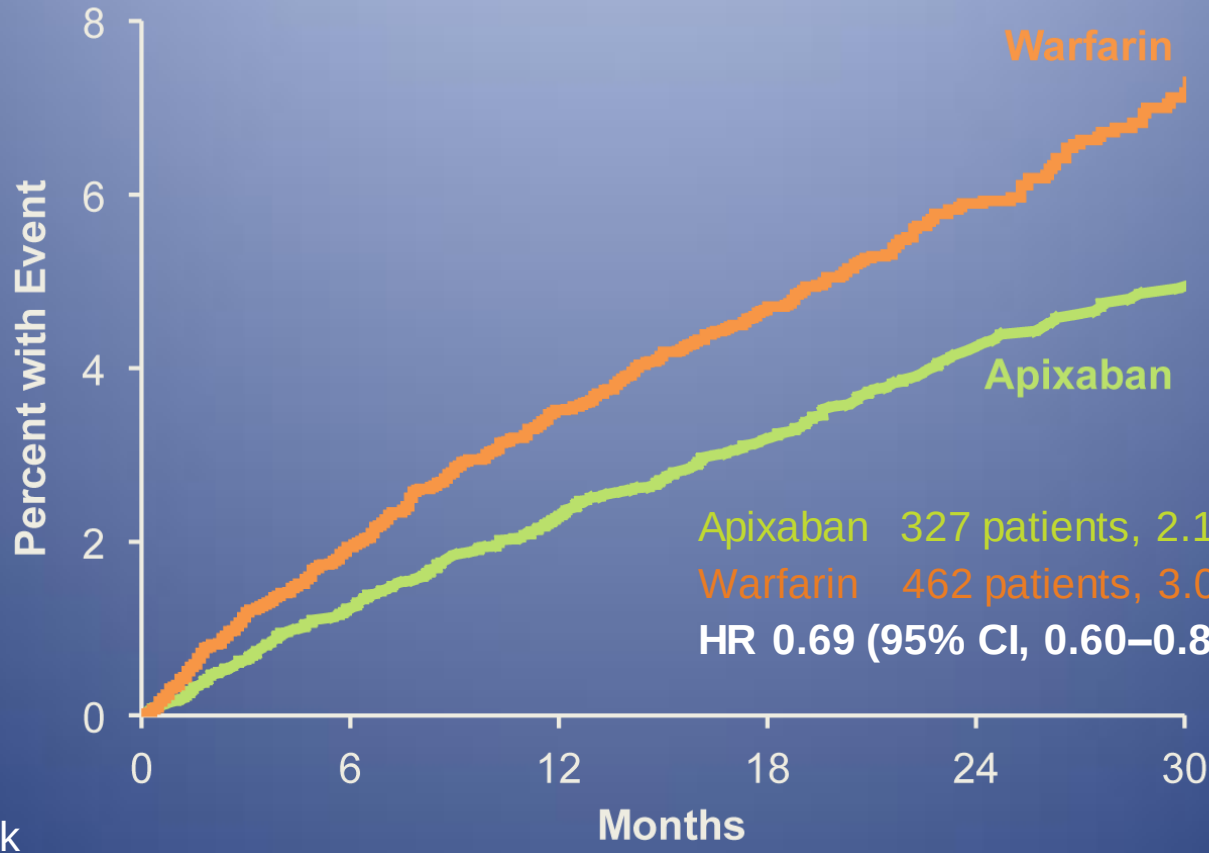
No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

ARISTOLTE - Efficacy Outcomes

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

ARISTOTLE- Major Bleeding

ISTH definition



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

Compared with warfarin, apixaban (over 1.8 years) prevented

- 6 Strokes
  - 4 hemorrhagic
  - 2 ischemic/uncertain type
- 15 Major bleeds
- 8 Deaths

per 1000 patients treated.

ARISTOLTE - Summary

Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

- Reduces stroke and systemic embolism by 21% (p=0.01)
- Reduces major bleeding by 31% (p<0.001)
- Reduces mortality by 11% (p=0.047)

with consistent effects across all major subgroups and with fewer study drug discontinuations on apixaban than on warfarin, consistent with good tolerability.

Apixaban

- Approved by FDA December 31, 2012
- Only US Indication is for Non-Valvular Afib
- About $220 a month / $5 pill

ARISTOTLE - Conclusion

In patients with atrial fibrillation, apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding, and results in lower mortality.

Original Article

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators

N Engl J Med
Volume 369(22):2093-2104
November 28, 2013

The NEW ENGLAND JOURNAL of MEDICINE

Study Design

21,105 PATIENTS
AF on electrical recording within last 12 m
$CHADS_2$ ≥2

RANDOMIZATION
1:1:1 randomization is stratified by $CHADS_2$ score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

Warfarin (INR 2.0–3.0)	High-dose Edoxaban 60* mg QD	Low-dose Edoxaban 30* mg QD

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

1º Efficacy EP = Stroke or SEE
2º Efficacy EP = Stroke or SEE or CV mortality
1º Safety EP = Major Bleeding (ISTH criteria)

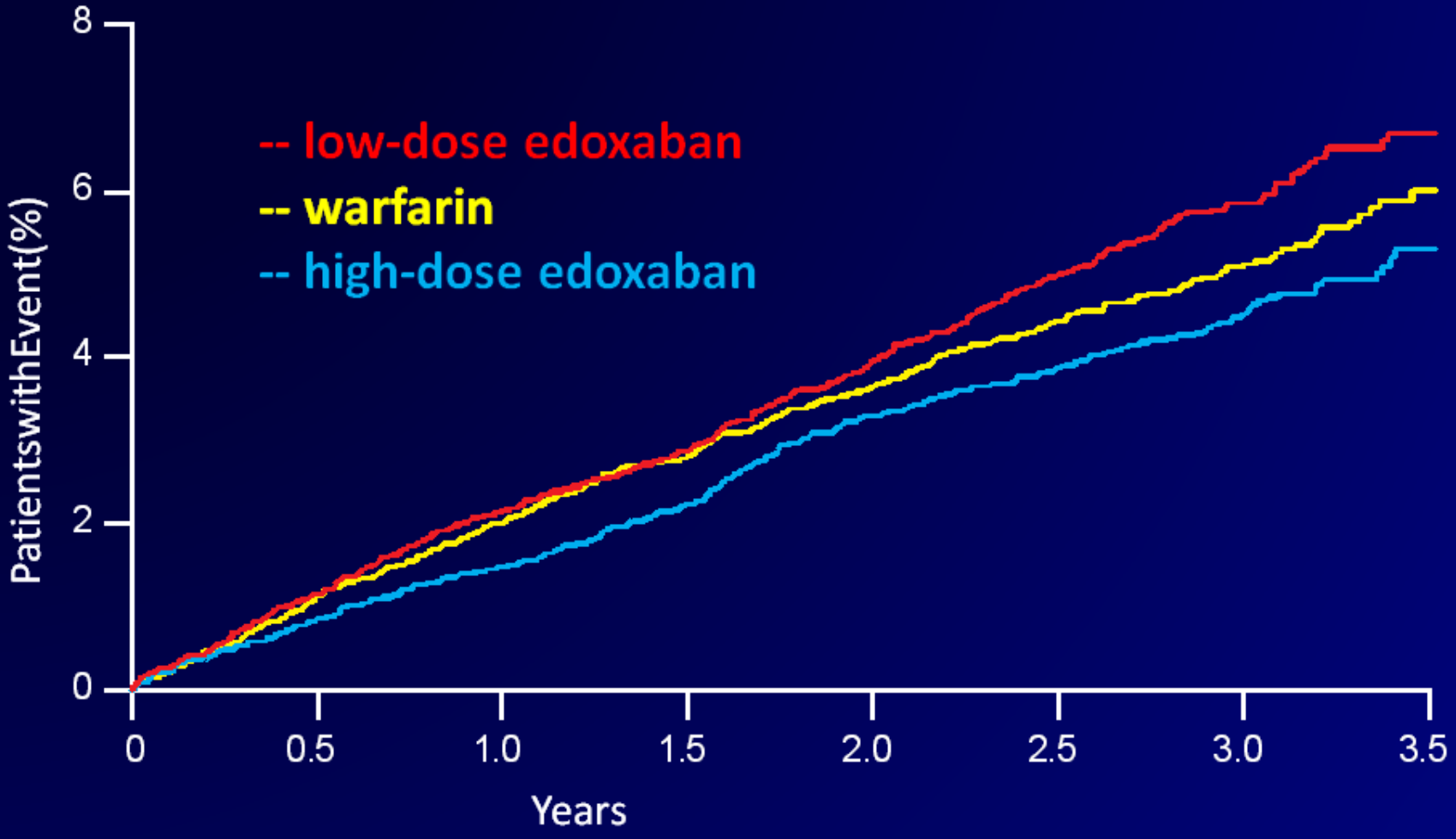
Non-inferiority
Upper 97.5% CI <1.38

CI = confidence interval; CrCl = creatinine clearance; ISTH=International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE=systemic embolic event

Ruff CR et al. Am Heart J 2010; 160:635-41.

Variable	Warfarin (n=7,036)	High-dose edoxaban (n=7,035)	Low-dose edoxaban (n=7,034)
Median age, years	72	72	72
Female sex, n (%)	2,641 (37.5)	2,669 (37.9)	2,730 (38.8)
Qualifying risk factors, n (%)			
Age ≥75 years	2,820 (40.1)	2,848 (40.5)	2,806 (39.9)
Prior stroke or TIA	1,991 (28.3)	1,976 (28.1)	2,006 (28.5)
Congestive heart failure	4,048 (57.5)	4,097 (58.2)	3,979 (56.6)
Diabetes mellitus	2,521 (35.8)	2,559 (36.4)	2,544 (36.2)
Hypertension	6,588 (93.6)	6,591 (93.7)	6,575 (93.5)
$CHADS_2$ score			
Mean score ± SD	2.8±1.0	2.8±1.0	2.8±1.0
2–3, n (%)	5,445 (77.4)	5,422 (77.1)	5,470 (77.8)
4–6, n (%)	1,591 (22.6)	1,613 (22.9)	1,564 (22.2)

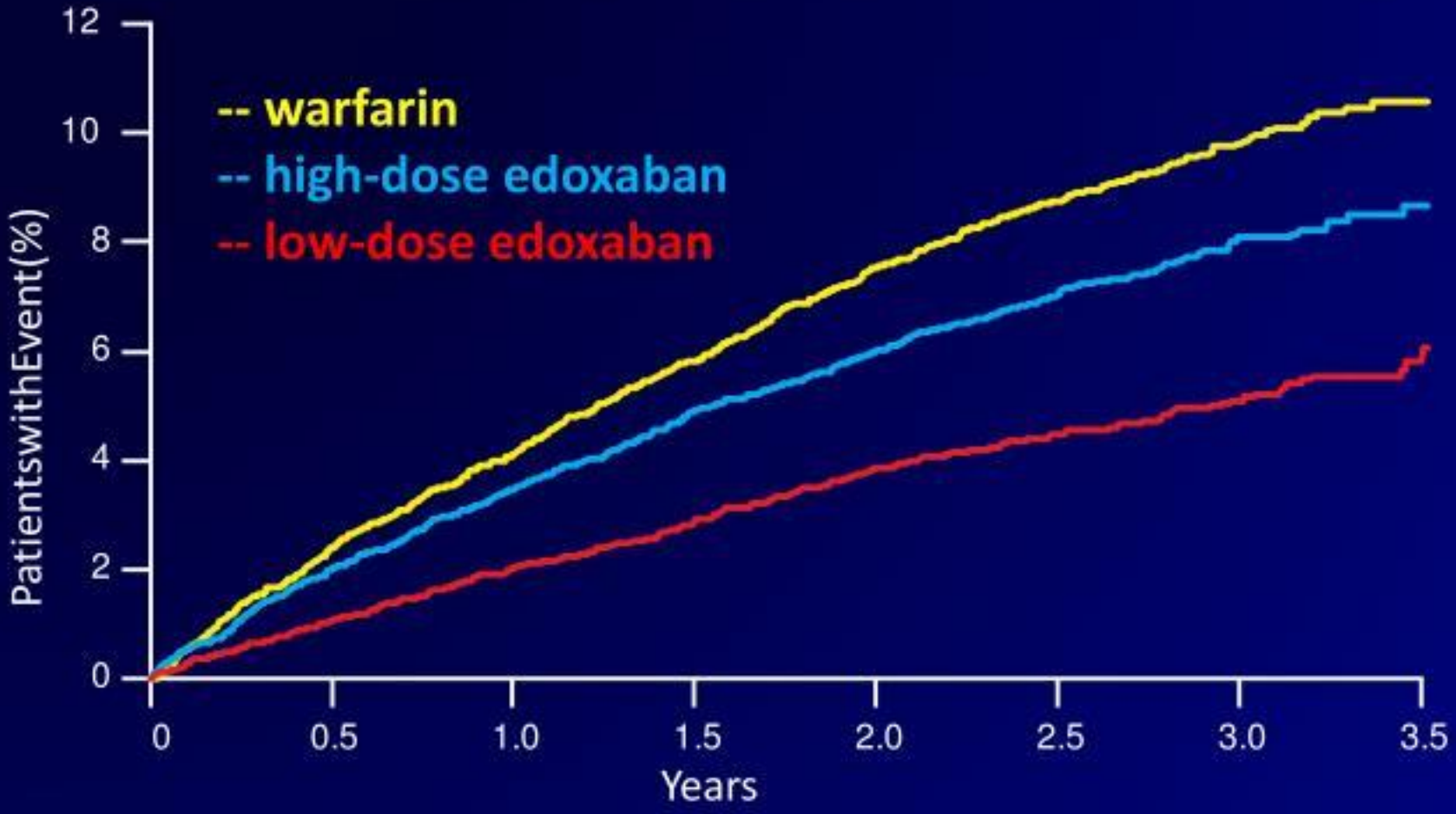
ENGAGE: event rates with edoxaban or warfarin, after up to 3.5 years



Guigliano *et al.*, NEJM 2013

ENGAGE: major bleeding rates with edoxaban or warfarin, up to 3.5 years

CardioVasculaire GeneesKunde.nl



Guigliano *et al.*, NEJM 2013

Conclusions

- Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

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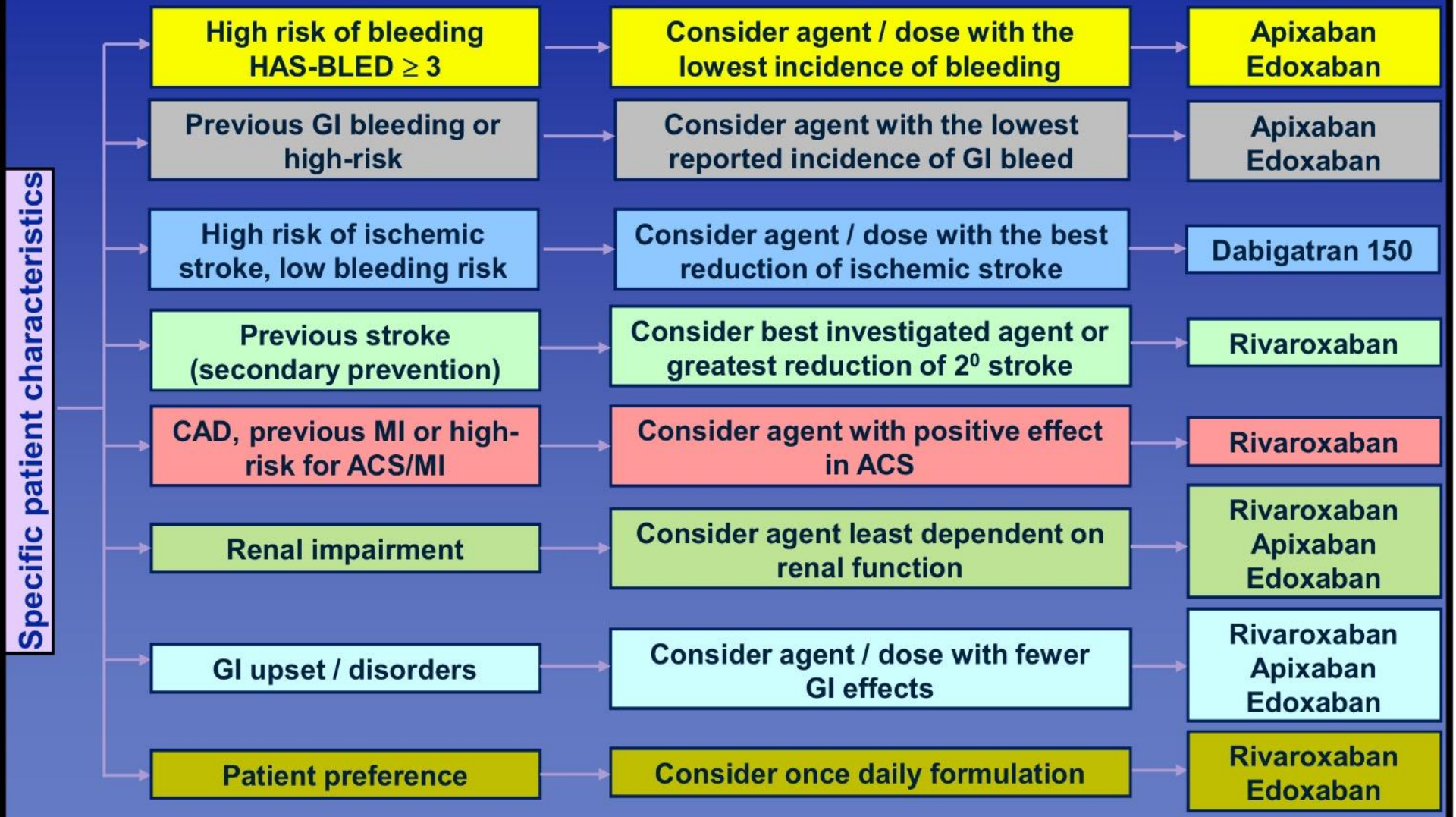
COMPARISON OF TRIALS

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Total Patients	18,113	14,264	18,201	21,105
Randomized treatment grps	Dabigatran 110mg BID or 150mg BID	Rivaroxaban 20mg QD	Apixaban 5mgBID	Edoxaban 30mgBID or 60mg BID
Mean CHADS2VASC	2.1	3.5	2.1	2.8
Therapeutic INR	64%	55%	62%	68%
Dose Adjustment	None	15mg QD for CrCl 30-49mL/min	2.5mg BID for ≥ 2 of the following: ≥ 80y/o ≤60kg Cr≥1.5	Dose Halved for ≥ 1 of the ff: CrCl 30-50mL/min Wt ≤ 60kg Verapamil/multaq

SUMMARY OF PHASE III NOAC TRIAL

OUTCOMES VS WARFARIN	DABIGATRAN 150MG BID	RIVOROXABAN	APIXABAN	EDOXABAN 60MG QD
Stroke/systemic embolism	Superiority	Non-inferiority Equivalent	Superiority	Non-inferiority Equivalent
Ischemic Stroke	↓	↔	↔	↔
Hemorrhagic Stroke	↓	↓	↓	↓
ICH/Fatal Bleeding	↓	↓	↓	↓
GIB	↑	↑	↓	↓
Major Bleed	↔	↔	↓	↓
All Cause Mortality	↔	↔	↓	↓

Considerations in NOAC Selection for AF



Modified after Savalieva I, Camm AJ. *Clin Cardiol* 2014; 37: 32

So I need Surgery/Procedure

TABLE 2

How long to delay elective surgery or procedures after last anticoagulant dose

Anticoagulant drug	Creatinine clearance (mL/min)	Low-risk surgery [a]	High-risk surgery [b]
Dabigatran	> 50	24 hours	2 days
	31–50	2 days	4 days
	≤ 30	4 days	6 days
Rivaroxaban	> 30	24 hours	2 days
	≤ 30	2 days	4 days
Apixaban	> 30	24 hours	2 days
	≤ 30	2 days	4 days

[a] Examples include cardiac catheterization, diagnostic endoscopy, breast biopsy, and minor orthopedic procedures

[b] Examples include cardiac surgery, vascular surgery, spinal or neurosurgery, and abdominal surgery

KEY POINTS FOR NVAF

- Warfarin is superior to ASA and placebo for 2nd stroke prevention
  - DOAC's are superior to Warfarin
  - Aspirin should not be used for prevention
  - Combination of DOAC and ASA increases bleeding risk and should be restricted
- Anticoagulation is a contraindication to thrombolysis in the setting of acute ischemic stroke... consider mechanical thrombectomy

KEY POINTS FOR NVAF

- OAC MAY BE INITIATED AFTER NEUROIMAGING HAS EXCLUDED ICH
  - TIA ON THE 1ST DAY AFTER EVENT
  - MINOR STROKE: 3 DAYS
  - MODERATE STROKE: 5-7 DAYS
  - SEVERE STROKE: 12-14 DAYS
- FOR PATIENTS WITH HIGH RISK FOR GIB
  - APIXABAN OR DABIGATRAN 110MG BID
  - RISK OF GIB INCREASED WITH CONCURRENT ANTIPLATELET AND AGE>75

KEY POINTS FOR NVAF

- CKD
  - CrCl 30-49ml/min: Apixaban 2.5mgBID, Rivaroxaban 15mg QD or Edoxaban 30mg QD
  - Hemodialysis no anticoagulation or Coumadin
  - CrCl>95ml/min, Edoxaban 60mg QD should not be utilized
- AGE > 75years
  - Apixaban 2.5mg BID first line, Dabigatran 110mg BID, Rivaroxaban 20mg QD, Edoxaban 60mg QD

KEY POINTS FOR NVAF

- 30% WILL HAVE CONCOMITTANT CAD
  - Monotherapy with DOAC is preferable
  - Add ASA based on individual risk assessment
  - PCI who require triple therapy, Warfarin is preferred
  - DOAC may be chosen
- CARDIOVERSION is associated with 5-7% risk of Thromboembolic events within a month
  - Warfarin remains standard of care
  - DOACs are safe and effective, ongoing trials

KEY POINTS FOR NVAF

- CONCOMMITANT USE WITH ANTIARRHYTHMIC MEDICATIONS
  - Dabigatran and Edoxaban should be reduced with Verapamil
  - Dabigatran is contraindicated with Dronedarone
  - Edoxaban reduced to 30mg QD with Dronanedarone

CONCLUSION

- All four DOAC's were SUPERIOR to warfarin in hemorrhagic stroke reduction
- All four DOAC's are superior or noninferior to warfarin in reducing overall stroke
- The risk of serious bleeding is reduced with all four DOAC's
- All 4 drugs rapid onset, short half lives

CONCLUSION

- Pradaxa has high renal clearance
- All drugs need a dose reduction for low CrCl
- All drugs have a black box to BRIDGE with lovenox/heparin after stopping
- Pradaxa has known higher GI side effects
- All have indications in DVT/PE treatment
- Xarelto, Pradaxa,Eliquis has indication for DVT/PE prophylaxis
- All have high/variable costs to the patient
- Doctor – patient discussion about stroke risk, bleeding risk, and all options.

CONCLUSION

- In all three trials, the Warfarin arm had therapeutic INR at most 66% of the time
  - This means in the real world, it is much less
- Pradaxa and Eliquis trials had CHADS 0-1 patients with a mean CHADS score of 2.1
- Xarelto trial Mean CHADS score was 3.5 (higher risk patients)
- Savaysa trial Mean CHADS score was 2.8
- Eliquis and Savaysa have a mortality benefit
- Xarelto and Savaysa are dosed once daily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ARISTOTLE - Bleeding Outcomes

Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) Event Rate (%/yr)	HR (95% CI)	P Value
Primary safety outcome: ISTH major bleeding*	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61, 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35, 0.60)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46, 0.70)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68, 0.75)	<0.001

ARISTOLE - Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Qualifying risk factors, %		
Age ≥75 yrs	31	31
Prior stroke, TIA, or SE	19	20
Heart failure or reduced LV EF	35	36
Diabetes	25	25
Hypertension	87	88
Renal function (Cl_{Cr} ml/min), %		
Normal (>80)	41	41
Mild impairment (>50 – 80)	42	42
Moderate impairment (>30 – 50)	15	15
Severe impairment (≤ 30)	1.5	1.5

ARISTOTLE - Objectives

Primary objective

- To determine whether apixaban is non-inferior to warfarin at reducing stroke (ischemic or hemorrhagic) or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

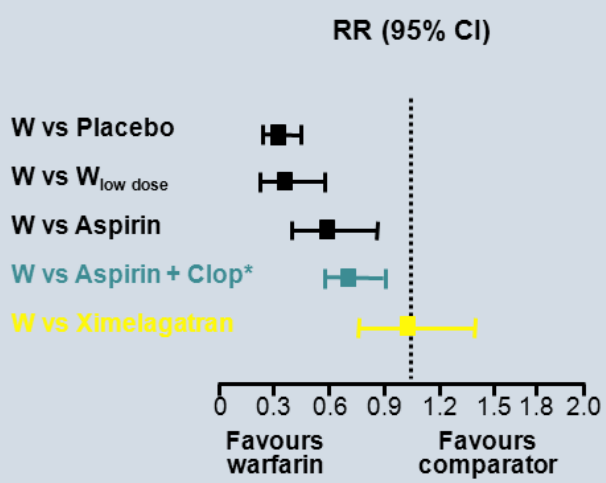
Primary safety outcome

- Major bleeding according to the International Society of Thrombosis and Hemostasis (ISTH) definition.
  - 2 gram drop in Hemoglobin
  - 2 units of transfusion
  - Bleeding in critical organ
  - Death

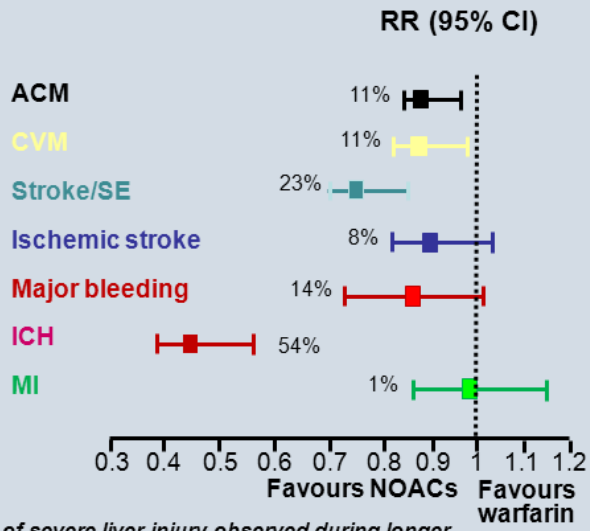
Efficacy and Safety of NOACs vs. Warfarin

Systematic reviews and meta-analyses

Stroke or SE in trials of warfarin vs comparators[19]



NOACs vs warfarin in 'modern' phase II/III trials (n = 54,875)[20]



Development of ximelagatran was terminated in 2006 because of severe liver injury observed during longer term treatment..

ACM, all-cause mortality; CVM, cardiovascular mortality; ICH, intracranial haemorrhage; MI, myocardial infarction; RR, relative risk; SE, systemic embolism; W, warfarin

For references, see text.

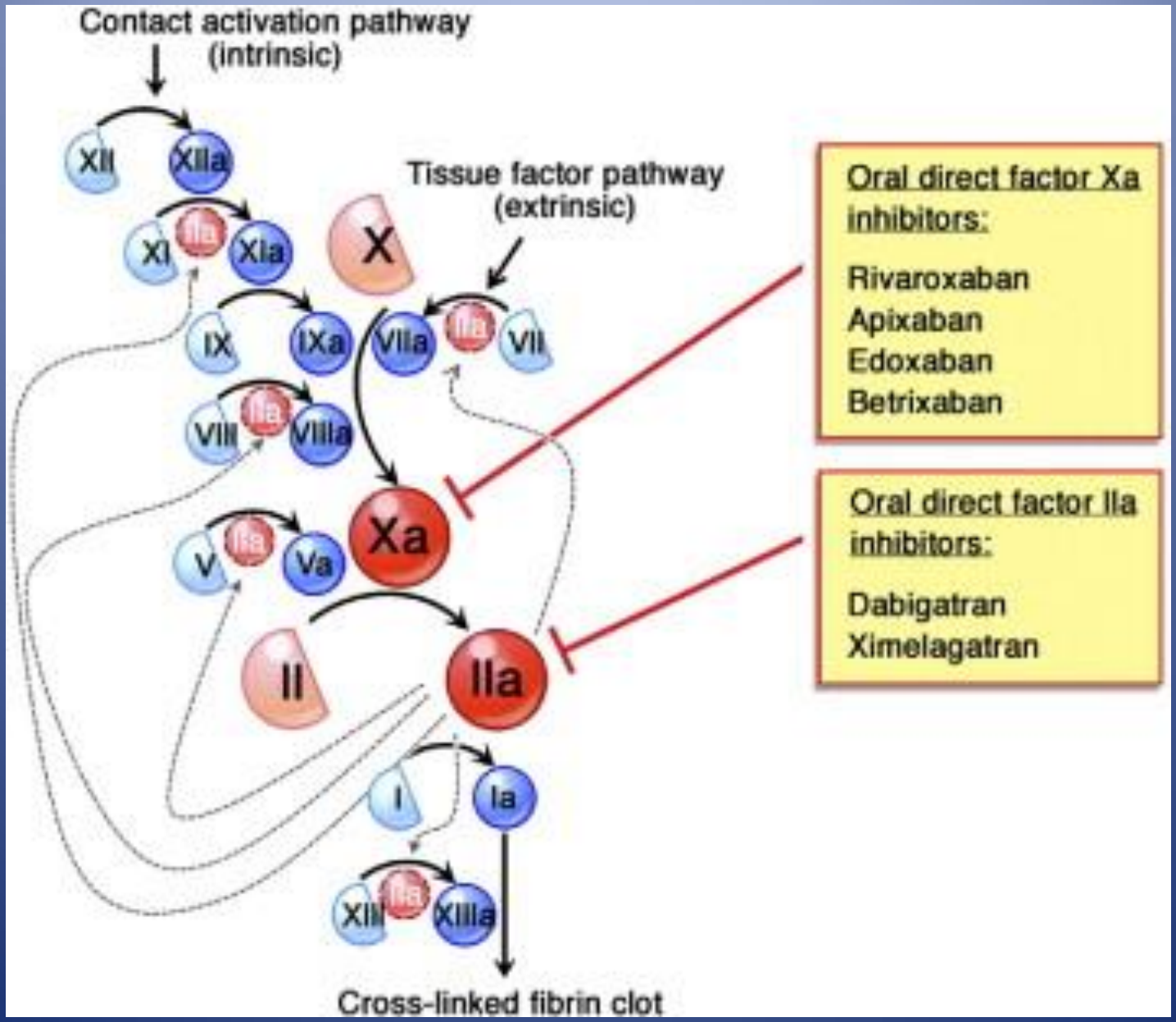
Dentali F. Circulation 2012;126: 2381-2391

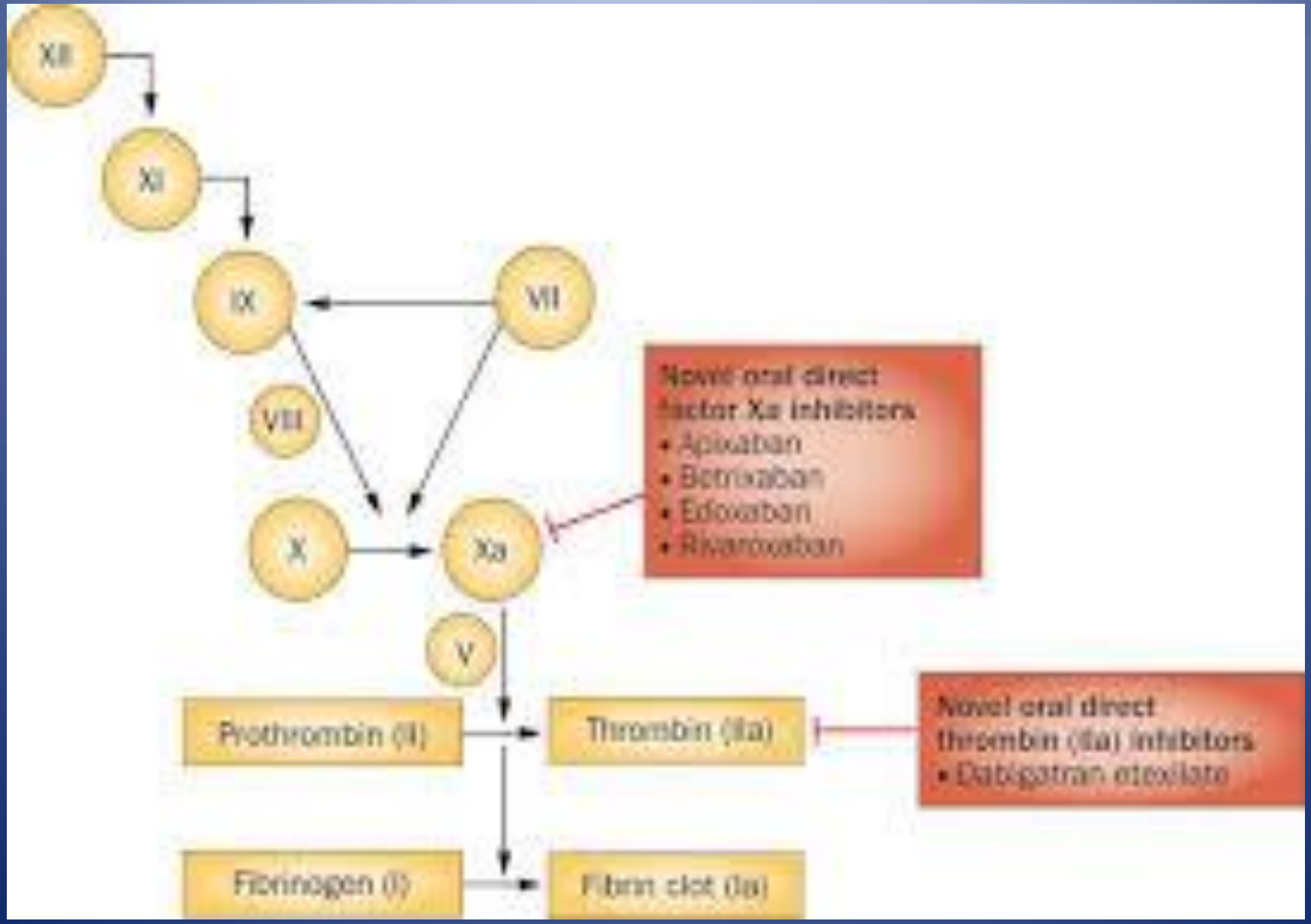
ARISTOTLE - Trial Metrics

- Patients enrolled from December 2006 to April 2010
- Median duration of follow-up 1.8 years
- Drug discontinuation in 25.3% of apixaban and 27.5% of warfarin patients (p=0.001)
- Vital status at the end of the trial was missing in 380 (2.1%) patients
  - Withdrawal of consent in 199 patients
  - Loss to follow-up in 69 patients
- Median (and mean) times in therapeutic INR range among warfarin- treated patients were 66.0 (and 62.2)%.

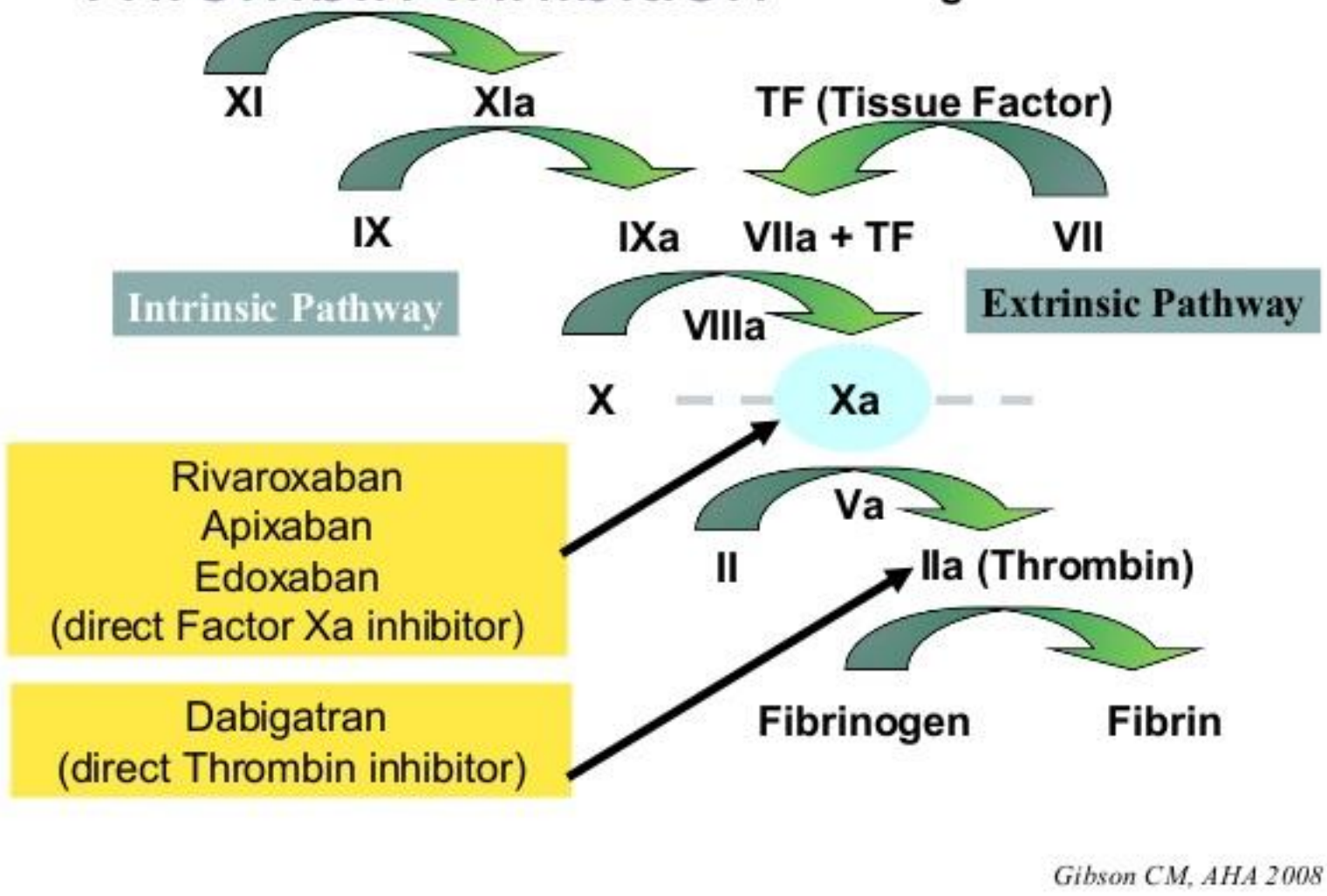
OAC/DOAC

- DABIGATRAN/PRADAXA: Direct Thrombin Inhibitor
- RIVAROXABAN/XARELTO: Factor Xa Inhibitor
- APIXABAN/ELIQUIS: Factor Xa Inhibitor
- EDOXABAN/SAVAYSA: Factor Xa Inhibitor


Contact activation pathway
(intrinsic)
XII
XIIa
XI
XIa
IX
IXa
VIII
VIIIa
V
Va
II
IIa
Tissue factor pathway
(extrinsic)
X
VIIa
VII
Xa
I
Ia
XIII
XIIIa
Cross-linked fibrin clot
Oral direct factor Xa inhibitors:
Rivaroxaban
Apixaban
Edoxaban
Betrixaban
Oral direct factor IIa inhibitors:
Dabigatran
Ximelagatran


XII
XI
IX
VII
VIII
X
Xa
V
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin clot (Ia)
Novel oral direct
factor Xa inhibitors
• Apixaban
• Betrixaban
• Edoxaban
• Rivaroxaban
Novel oral direct
thrombin (IIa) inhibitors
• Dabigatran etexilate

Thrombin Inhibition



Gibson CM, AHA 2008

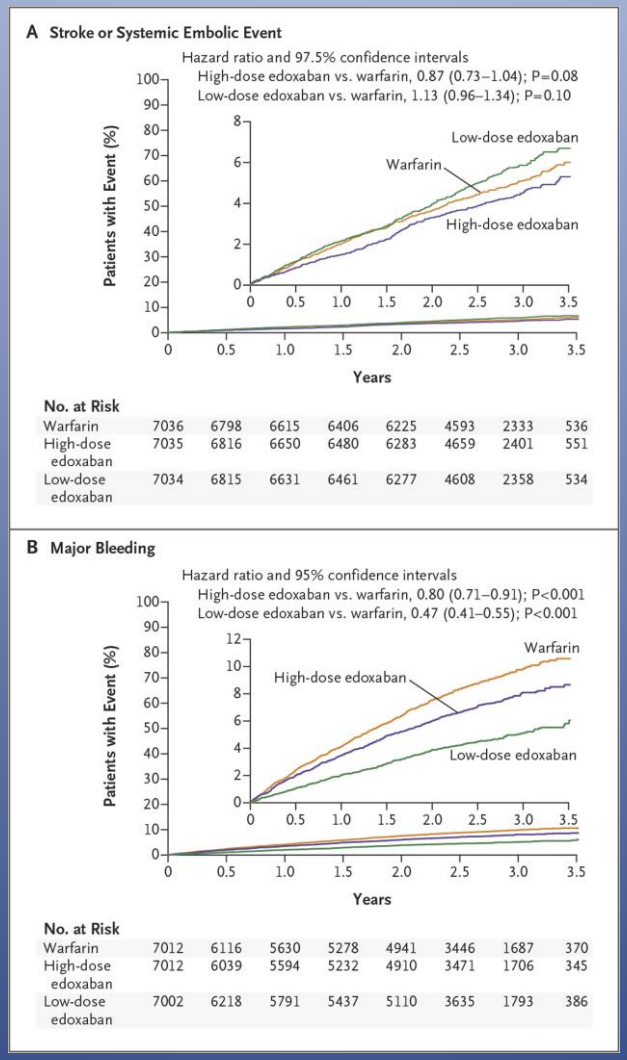
TABLE 1

Table 1. Pharmacological characteristics of the main NOACs

DRUG	DABIGATRAN ETEXILATE	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism of action	direct thrombin inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor
Oral bioavailability	6.5%	80-100%	50%	62%
Time to max inhibition	0.5-2 h	1-4 h	1-4 h	1-2 h
Half-life	12-14 h	5-13 h	8-15 h	10-14 h
Renal excretion (fraction of absorbed dose)	85%	66% (36% unchanged and 30% inactive metabolites)	27%	50% (of the absorbed drug)
Potential metabolic drug interaction	Inhibitors of P-gp: verapamil --> reduce dose; dronedarone --> avoid Potent inducers P-gp*: avoid	Potent inhibitors of CYP3A4# and P-gp†: avoid Potent inducers of CYP3A4‡ and P-gp*: use with caution	Potent inhibitors of CYP3A4# and P-gp†: avoid Potent inducers of CYP3A4‡ and P-gp*: use with caution	Potent inhibitors of P-gp†: reduce dose Potent inducers of P-gp*: avoid
Dose in VTE prevention and treatment°	220 mg OD or 150 mg OD (prev.) 150 BID (treat.)	10 mg OD (prev.) 15 mg BID, then 20 mg OD (treat.)	2.5 mg BID (prev.) 5 mg BID (treat.)	60 mg OD (treat.)
Dose in AF°	110 mg BID or 150 mg BID	20 mg OD or 15 mg OD for CrCl 30-49	5 mg BID or 2.5 BID for risk categories	60 mg OD (30 mg for risk categories) or 30 mg OD (15 mg for risk categories)
Dose in ACS°		2.5 BID		

* Rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, phenytoin
# Antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin and protease inhibitors (e.g., ritonavir, atanazavir)
† Verapamil, amiodarone, quinidine and clarithromycin
‡ Phenytoin, carbamazepine, phenobarbital and St. John's wort
° Phase III clinical trials - Results for ENGAGE-AF still pending, therefore in this case the dosages do not refer to approved use
CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein; OD = once daily, BID = twice daily

Kaplan–Meier Curves for the Primary Efficacy and Principal Safety End Points.



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

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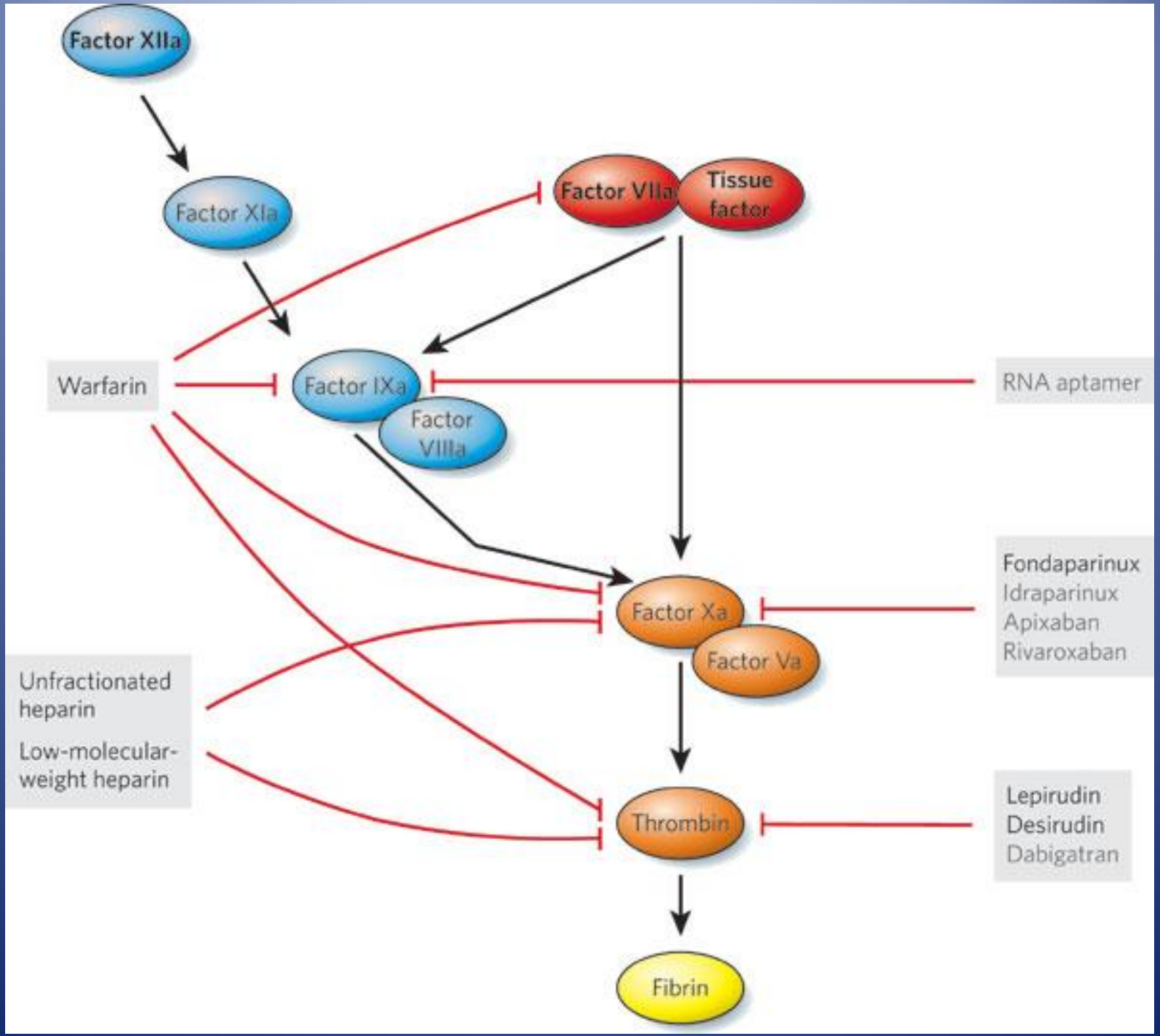
Pharmacology Summary

TABLE 1

Pharmacokinetic profiles and metabolism of the new oral anticoagulants

Feature	Dabigatran	Rivaroxaban	Apixaban
Prodrug	Yes	No	No
Mode of action	Thrombin inhibition	Factor Xa inhibition	Factor Xa inhibition
Bioavailability	6%–8%	80%	50%
Time to peak	1.5–2 hours	2–3 hours	3 hours
Half-life	14–17 hours	7–11 hours	8–14 hours
Excretion	Renal (unchanged) > 80% Bile 5%–10%	Renal (half inactive) 66% Feces 33%	Renal 25%–30% Feces 56%
Plasma protein binding	35%	95%	87%

DATA FROM REFERENCES 13, 16, AND 18.

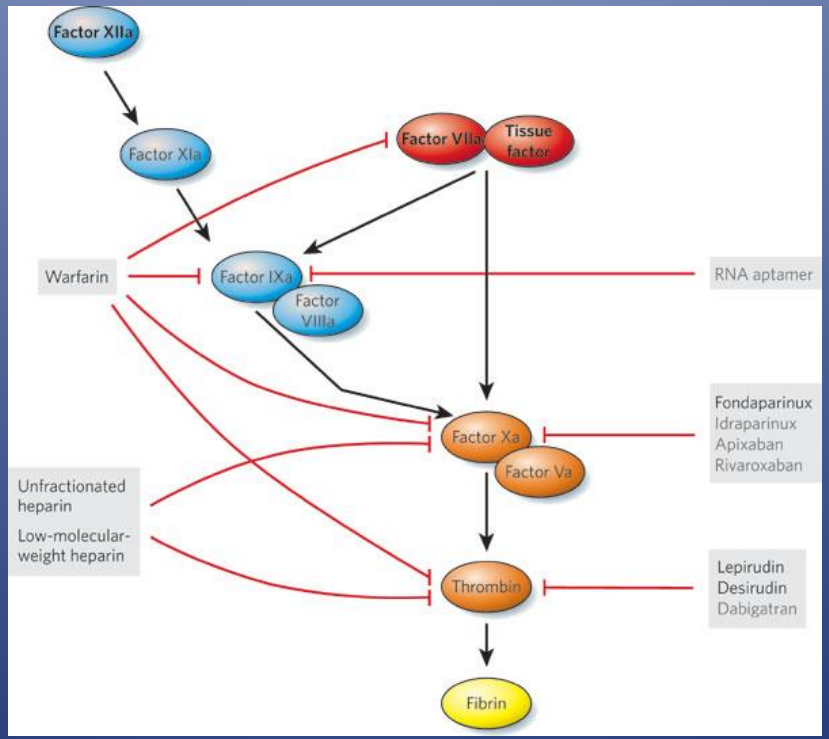

Factor XIIa
Factor XIa
Factor VIIa
Tissue factor
Warfarin
Factor IXa
Factor VIIIa
RNA aptamer
Fondaparinux
Idraparinux
Apixaban
Rivaroxaban
Factor Xa
Factor Va
Unfractionated heparin
Low-molecular-weight heparin
Thrombin
Lepirudin
Desirudin
Dabigatran
Fibrin

How to Control bleeding

- Time – all the new agents have short half lives
- Fresh Frozen Plasma – Vit K factors; 2, 7, 9, 10
- Recombinant Factor VIIa – initiates thrombin generation via Factor X activation
- Prothrombin Complex Concentrates (PCC) – virus reduced, concentrated, pooled plasma products with 3 or 4 vit K dependent factors
  - Bebulin and Profilnine (low non active Factor VII with predominate 2, 9, 10)
  - Beriplex (Factors 2, 7, 9, 10) – stimulate thrombin

How to Control Bleeding

- Activated PCC (aPCC) – freeze dried sterile human plasma factions.
  - FEIBA NF – activated Factor VII with non-active 2, 9, 10



Factor Xa Reveral Options (Xarelto/Eliquis)

- Can follow the PT
- FFP not recommended
- Recombinant Factor VIIa – animal studies only, not recommended
- PCCs – Study in 2011 showed 50 IU/kg PCC bolus would reverse Xa agent. **Officially recommended agent**

Pradaxa Reversal

- Follow aPTT
- Hemodialysis can remove 60% of drug in 2-3 hours (limited real life data)
- FFP is not recommended
- Recombinant Factor VIIa – some data it can work, but no clinical data
- PCC – some animal data, no human data

Table 2. Mechanisms of Action of Anticoagulation Reversal Agents

Reversal Agent	Mechanism of Action	Role in Reversal	
		Rivaroxaban	Dabigatran
PCC	Replaces deficient clotting factors. Factor IX is activated by factor XIa in the intrinsic coagulation pathway. Activated factor IX (IXa) in combination with factor VII:C activates factor X to Xa, resulting in the conversion of prothrombin to thrombin and the formation of a fibrin clot. The infusion of exogenous factor IX to replace the deficiency restores hemostasis.[25]	Data in healthy volunteers suggest a dose of 50 U/kg	Data in healthy volunteers do not demonstrate efficacy based on coagulation parameters
aPCC (FEIBA®)	aPCCs contain prothrombin, FVII, FIX, FX, and protein C; the zymogen forms of important hemostatic enzymes and very small amounts of their activation products, except for FVIIa, which is contained in greater amounts. The mechanism of action comprises multiple biochemical interactions, which induce or facilitate thrombin generation even in the absence of FVIII.[11]	Animal data available for the use of FEIBA for the reversal of rivaroxaban	No data exist
rVIIa	aFVII binds to the TF that is found on the surface of subendothelial cells. TF-FVIIa complex then activates FIX and FX, which leads to the formation of a small initial amount of thrombin. Thrombin activates blood platelets and other coagulation factors (FV and FVIII), resulting in the "thrombin burst." This large amount of thrombin then enables the conversion of fibrinogen to fibrin and the formation of a fibrin clot.[26]	Not recommended	No data in human patients or volunteers, but reversed bleeding in rat tail model
FFP	FFP is the plasma separated from a unit of whole blood. Each bag has a volume of 175 to 250 mL. FFP is used to replace coagulation factors. FFP contains an average of 1 IU/mL of all the coagulation proteins, including the labile factors V and VIII, and 400 to 800 mg of fibrinogen. It also contains fibrinolytic and complement factors.[11]	Not recommended	Not recommended

Holding New Agents

All three agents do carry the following BLACK BOX WARNING

"increase thrombotic event and stroke risk when discontinuing (pick your agent) in patients with non-valvular afib; if must d/c (pick your agent) for reasons other than pathological bleeding, consider administering another anticoagulant"

Use a Lovenox or heparin bridge for 24-48 hrs after stopping the drug

Original Article

Idarucizumab for Dabigatran Reversal

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NOACs Phase 3 Trials
Mean $CHADS_2$ Scores

Trial	Mean $CHADS_2$
ARISTOTLE[a] apixaban vs warfarin	2.1 ± 1.1
ENGAGE AF-TIMI 48[b] edoxaban vs warfarin	2.8 ± 1.0
RE-LY[c] dabigatran vs warfarin	2.1 ± 1.1
ROCKET AF[d] rivaraxoban vs warfarin	3.48 ± 0.94 (rivaraxoban) 3.46 ± 0.95 (warfarin)

a. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[3]; b. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104[5]; c. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[4]; d. Patel MR, et al. *N Engl J Med*. 2011;365:883-891.[6]

Apixaban

- Drugs expected to significantly increase bleeding risk if coadministered:
  - Systemic treatment with strong inhibitors of both CYP3A4 and P-gp (e.g., ritonavir, ketaconazole)
  - Other anticoagulants
  - Antiplatelet agents and NSAIDs including ASA

Rivaroxaban

- Drugs expected to significantly increase bleeding risk if coadministered:
  - Systemic treatment with strong inhibitors of both CYP3A4 and P-gp (e.g., ritonavir, ketaconazole)
  - Other anticoagulants
  - Dual antiplatelet therapy (ASA plus a thienopyridine)
- Caution to be taken when coadministering NSAIDs, including ASA
- Not recommended owing to lack of data:
  - Dronedarone

Dabigatran

- Drugs expected to significantly increase bleeding risk if coadministered:
  - Systemic treatment with ketoconazole, cyclosporine, itraconazole, or tacrolimus, or quinidine
  - Other anticoagulants
- Contraindicated:
  - Dronedarone
- Dose reduction recommended in patients with moderate renal impairment:
  - Receiving comedications that are strong P-gp inhibitors
  - Taking verapamil, ASA, and/or clopidogrel

Study Overview

- Intravenous idarucizumab, an antibody fragment of a human antibody specific for dabigatran, produced rapid reversal of the anticoagulant effect in patients with bleeding or an urgent surgical indication with no apparent toxic effects or rebound hypercoagulable state.

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Clinical Characteristics of the Patients.

Table 1. Clinical Characteristics of the Patients.*

Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — kg			
Median	70.5	73.0	71.9
Range	42.4–127.5	49.5–116.0	42.4–127.5
Creatinine clearance‡			
Value — ml/min			
Mean	59±33	65±36	62±35
Median	54	60	58
Range	16–187	11–171	11–187
Distribution — no. (%)			
<30 ml/min	5 (10)	7 (18)	12 (13)
30 to <50 ml/min	14 (27)	6 (15)	20 (22)
50 to <80 ml/min	16 (31)	11 (28)	27 (30)
≥80 ml/min	6 (12)	9 (23)	15 (17)
Missing data	10 (20)	6 (15)	16 (18)
Dose of dabigatran — no. (%)			
150 mg twice daily	14 (27)	15 (38)	29 (32)
110 mg twice daily	34 (67)	24 (62)	58 (64)
75 mg twice daily	1 (2)	0	1 (1)
Other	2 (4)	0	2 (2)
Indication for dabigatran — no. (%)			
Atrial fibrillation	47 (92)	39 (100)	86 (96)
Venous thromboembolism	1 (2)	0	1 (1)
Other	3 (6)	0	3 (3)
Time since last intake of dabigatran			
Median — hr	15.2	16.6	15.4
Distribution — no. (%)			
<12 hr	17 (33)	15 (38)	32 (36)
12 to <24 hr	21 (41)	10 (26)	31 (34)
24 to <48 hr	12 (24)	10 (26)	22 (24)
≥48 hr	1 (2)	4 (10)	5 (6)
Elevated dilute thrombin time at baseline — no. (%)	40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline — no. (%)	47 (92)	34 (87)	81 (90)
Type of bleeding — no. (%)§			
Intracranial	18 (35)	—	18 (20)
Trauma-related	9 (18)	—	9 (10)
Gastrointestinal	20 (39)	—	20 (22)
Other	11 (22)	—	11 (12)

* Plus–minus values are means ±SD. Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was estimated by the Cockroft–Gault equation.
§ Patients may have had more than one type of bleeding.

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Conclusions

- Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

Summary of Phase III NOAC Trial Results

Outcomes *vs.* warfarin		Dabigatran 150 mg bid	Rivaroxaban	Apixaban	Edoxaban 60 mg qd
↓	Stroke/systemic embolism	Superiority	Non-inferiority	Superiority	Non-inferiority
↓	Stroke	Yes	No	Yes	Yes
↓	Ischemic or unspecified Stroke	Yes	No	No	No
↓	Hemorrhagic stroke	Yes	Yes	Yes	Yes
↓	Disabling or fatal stroke	Yes	No	Yes	Yes
↓	Vascular death	Yes	No	No	Yes
↓	All-cause mortality	No	No	Yes	No
↓	Major bleeding	No	No	Yes	Yes
↓	ICH	Yes	Yes	Yes	Yes
↑	GI bleeding	Yes	Yes	No	No
↓	Treatment discontinuation	No	No	Yes	Yes

Modified from Camm AJ, American Heart Association Scientific Sessions, Dallas, TX, November 2013

	RE-LY	ROCKET AF	AVERROES	ARISTOTLE	ENGAGE AF-TIMI 48
Total patients	18,113	14,264	5599	18,201	21,105
Randomized treatment groups	Dabigatran 110mg twice daily or 150mg twice daily	Rivaroxaban 20mg once daily	Apixaban 5mg twice daily	Apixaban 5mg twice daily	Edoxaban 30mg twice daily or 60 twice daily
Comparator	Dose-adjusted warfarin	Dose-adjusted warfarin	Aspirin	Dose-adjusted warfarin	Dose-adjusted warfarin
Blinded	No	Yes	Yes	Yes	Yes
Mean $CHADS_2$ Score	2.1	3.5	2.1	2.1	2.8
Prior stroke or TIA, %	20	55	14	19	28
Prior warfarin use, %	50	63	15	57	59
Median TTR (warfarin group), %	64 (mean)	58	N/A	66	68
Dose adjustments	None		15mg once daily for CrCl 30-49mL/min	2.5mg twice daily for ≥2 of the following: age ≥80 years, weight ≤60 kg, serum Cr ≥1.5 mg/dL	Dose halved for ≥1 of the following: CrCl 30-50mL/min, weight <60kg, concomitant use of verapamil, quinidine, or dronedarone

TIA = transient ischemic attack; TTR = time in therapeutic range (INR 2-3); N/A = not available.
From Connolly SJ, et al[20]; Patel MR, et al[34]; Connolly SJ, et al[41]; Granger CB, et al[42]; Giugliano RP, et al[44]; Wallentin L, et al.[54]

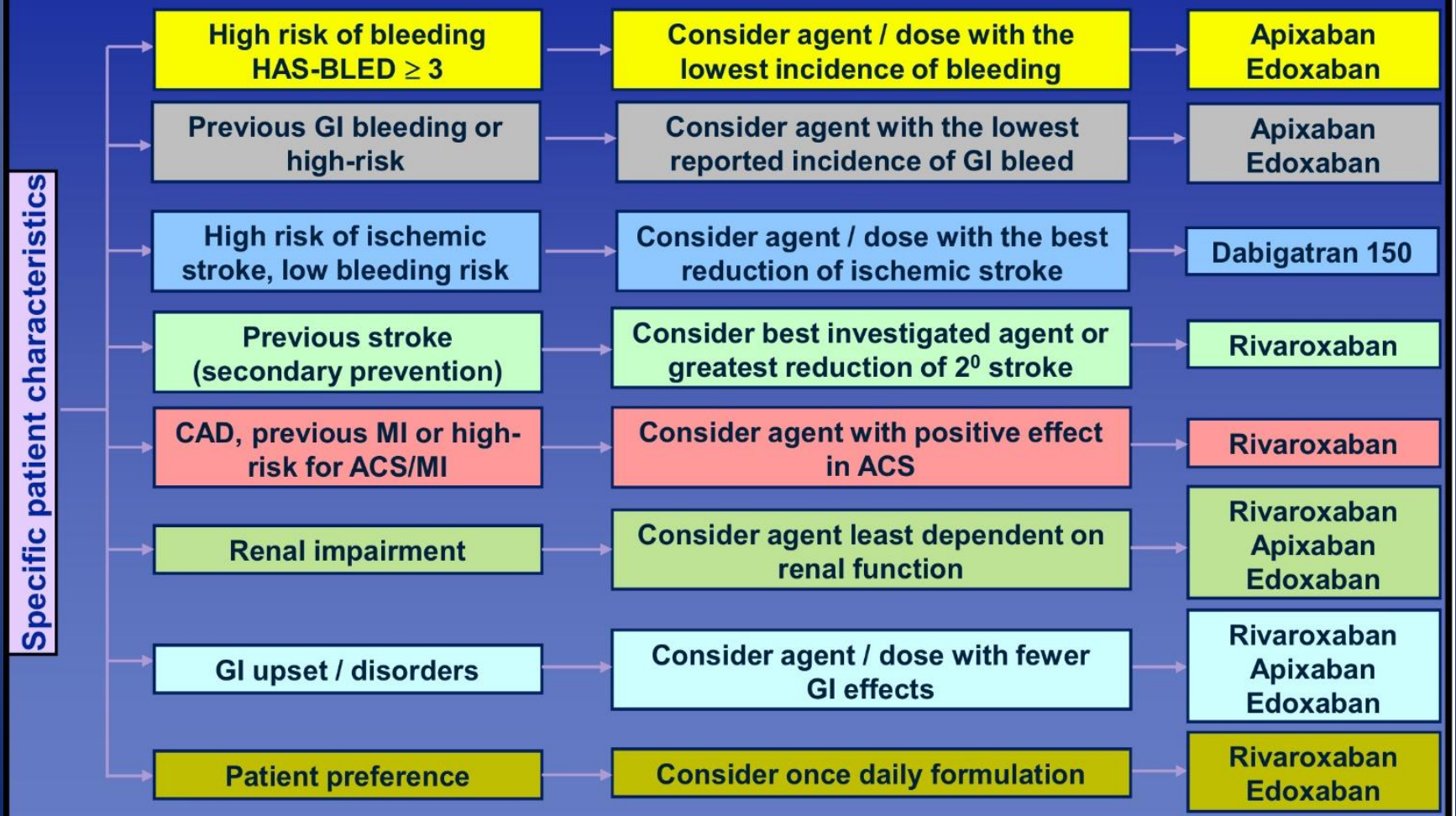
Comparison of new oral anticoagulants (NOACs)

	Dabigatran		Apixaban	Rivaroxaban
	150 mg BID	**110 mg BID**	**5 mg (2.5 mg) BID**	**20 mg (15 mg) OD**
Benefit over warfarin	Superior	Equivalent	Superior	Equivalent
Clinically significant reduction in ICH vs warfarin	Yes	Yes	Yes	Yes
Reduction in major bleeding vs warfarin	Equivalent	Yes	Yes	Equivalent
CrCl >50 ml/min	150 mg BID	110 mg BID	5 mg BID	20 mg OD
CrCl 30 – 49 ml/min	150 mg BID	110 mg BID	5 mg BID	15 mg OD
CrCl >25 ml/min	- - -	- - -	2.5 mg or 5 mg BID	- - -
CrCl >30 ml/min plus age ≥80 years	- - -	110 mg BID	2.5 mg or 5 mg BID	15 or 20 mg OD depends on CrCl
Special considerations	75 mg BID approved in USA for CrCl 15–29 ml/min, but not in Canada. No RCT data with this dose in patients with atrial fibrillation		Consider 2.5 mg BID if at least 2 of the following exists: 1) Age: ≥80 years 2) Weight: ≤60 Kg 3) Serum creatinine ≥133 (μM/L) (1.5 mg/dL)	
Antidote	• None available for NOACs • Vitamin K and PCC for warfarin. However, significant morbidity and mortality persists in patients with warfarin induced ICH despite rapid correction of INR • Pooled data from NOAC trials suggest ~50% reduction in ICH. Consequently for those using NOACs, there will be less ICH cases where "reversal therapy" would be required			
NOAC is not recommended with	• Mechanical valves • Valvular heart disease (primarily rheumatic heart disease/mitral stenosis) • Severe blood dyscrasias with clinically significant anemia, thrombocytopenia			

CrCl: Creatinine clearance; **ICH:** Intracranial hemorrhage; **INR:** International normalized ratio; **PCC:** Prothrombin complex concentrates; **RCT:** Randomized clinical trial

Refs: *Dowlatshahi D, et al. 2012. Stroke. 2012; 43:1812-1817*
Skanes AC, et al. Can J Cardiol 2012;28:125-136

Considerations in NOAC Selection for AF



Modified after Savalieva I, Camm AJ. *Clin Cardiol* 2014; 37: 32