ATRIAL FIBRILLATION-RELATED STROKE

Pathophysiology and conventional therapeutic strategies

ALPIC 2012

Advanced Learning on Platelets & Thrombosis International Course

Organized by:
Department of Cardiology, School of Medicine, University of Ioannina
Department of Chemistry, University of Ioannina
Under the auspices of:
Mediterranean League Against Thromboembolic Diseases
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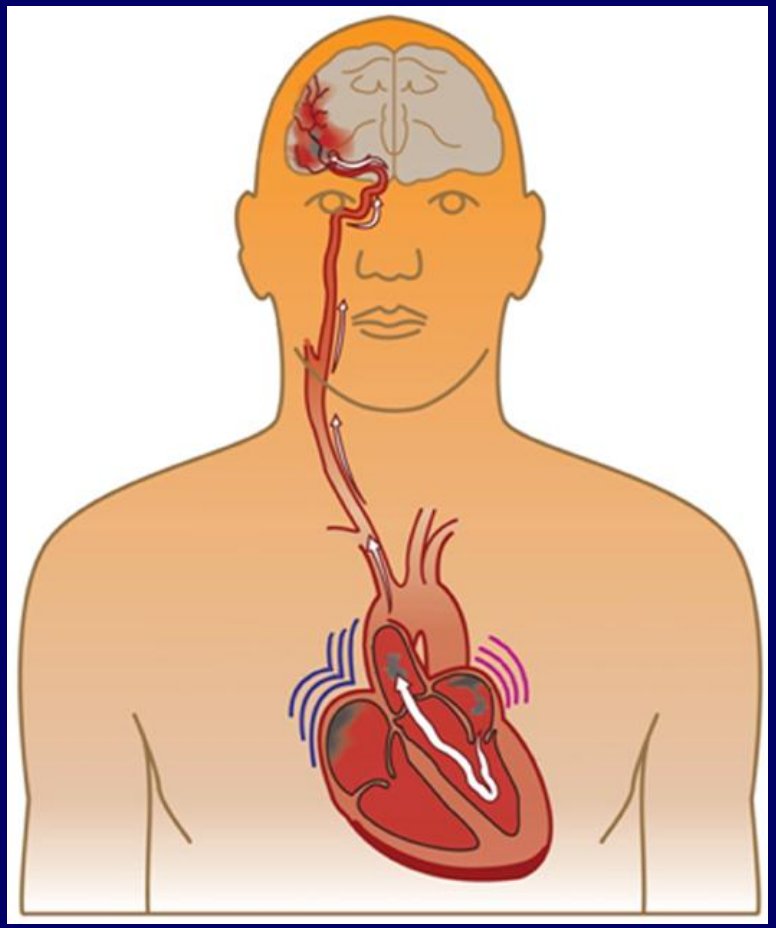
Stroke is the most common and devastating complication of AF

- AF is responsible for 15-20% of all ischaemic strokes[1]
- AF increases the risk of stroke 4- to 5-fold[2]
- AF is an independent risk factor for ischaemic stroke severity and recurrence[3]
- Stroke risk persists even in asymptomatic AF[4]



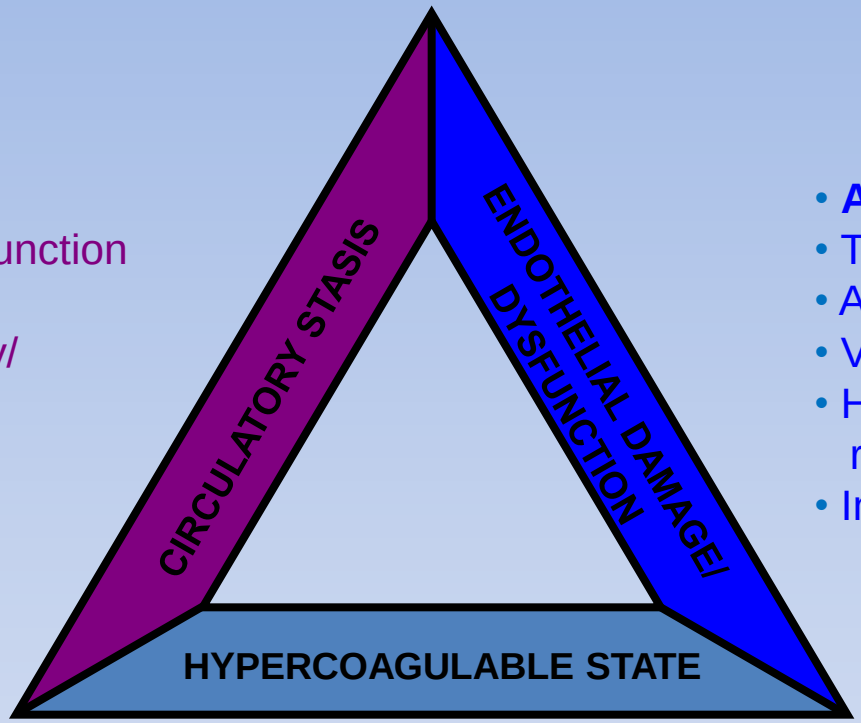
1. Go AS. *Am J Geriatr Cardiol.* 2005;14:56-61. 2. Wolf PA, *et al. Stroke.* 1991;22:983-988.
3. Penado S, *et al. Am J Med.* 2003;114:206-10. 4. Page RL, *et al. Circulation.* 2003;107:1141-1145.

Pathogenesis of clot formation in atrial fibrillation

- The pathogenesis of thromboembolism in AF is complex and multifactorial
- Extensive abnormal changes of the atrial wall, blood stasis and blood constituents are clearly evident in patients with AF
- Thus, AF could drive a prothrombotic or hypercoagulable state by virtue of its fulfilment of Virchow's triad for thrombogenesis

Virchow's triad

- **Atrial fibrillation**
- Left ventricular dysfunction
- Immobility
- Venous insufficiency/ varicose veins



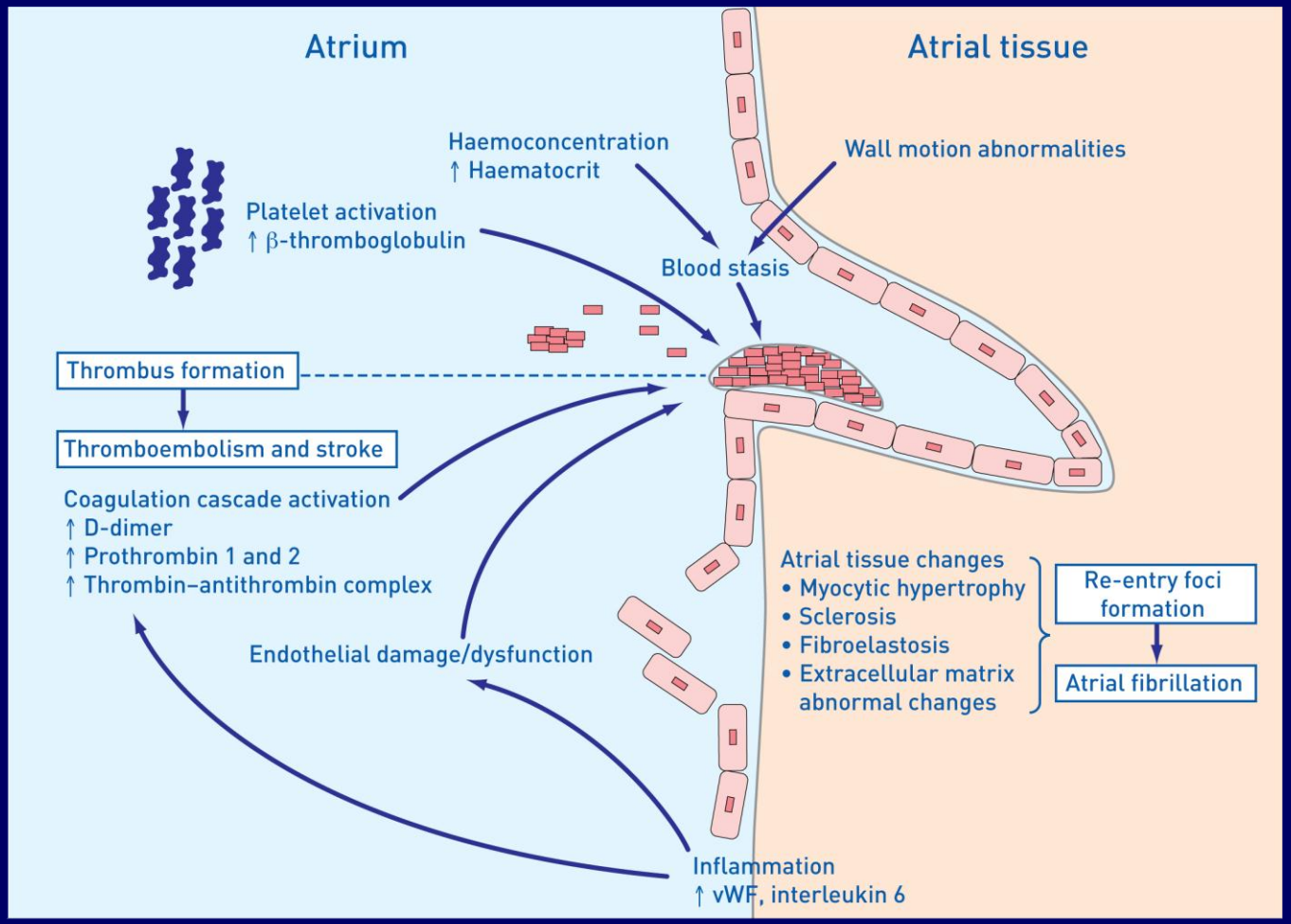
- **Atrial fibrillation**
- Trauma/surgery
- Atherosclerosis
- Venopuncture
- Heart valve disease/ replacement
- Indwelling catheters

- **Atrial fibrillation**
- Malignancy
- Pregnancy
- Oestrogen therapy
- Trauma/surgery

- Sepsis
- Thrombophilia
- Inflammatory bowel disease
- Nephrotic syndrome

Adapted from Watson T et al. Lancet 2009;373:155–66

Components of Virchow's triad for thrombogenesis in AF



Watson T et al. Lancet 2009;373:155–66

vWF = Von Willebrand factor

Blood stasis in AF

- Stasis is the most important cause of thrombosis in AF
- Erratic heart contraction reduces flow velocity in the atria (stasis), increasing the risk of thromboembolism
- Predictors of spontaneous echo contrast, a possible marker of stasis in AF, include:
  - Left atrial enlargement
  - Reduced left atrial appendage flow velocity
  - Left ventricular dysfunction
  - Fibrinogen level
  - Haematocrit

Abnormal changes of the atrial wall in AF

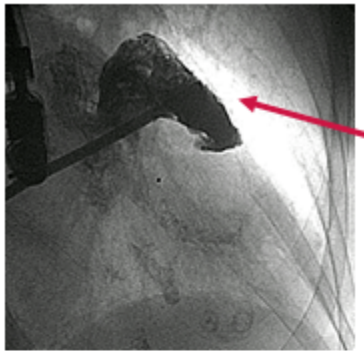
- AF causes enlargement of the left atrium and left atrial appendage (LAA)
- The LAA is the most common site of intra-atrial thrombus formation[1]
- Increased LAA width and length correlates with thromboembolic risk[2]

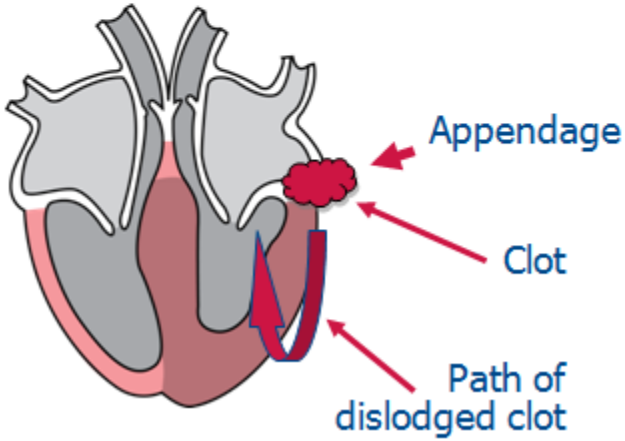
Hypercoagulable state in AF

- In AF, abnormal changes are evident in:
  - Platelets and proteins of the coagulation cascade
  - Inflammatory cytokines and growth factors
- Presence of a prothrombotic or hypercoagulable state in AF completes Virchow's triad
- Increased thrombogenesis has been reported in acute-onset or chronic AF[1–3]

Left atrial appendage and thrombus formation in AF

- Atria do not contract properly leading to stasis in the left atrium and appendage (LAA)
- LAA is a small muscular pouch attached to the main atrial chamber
- In non-valvular AF, ~90% of atrial thrombi occur in the LAA[1]





Non-cardioembolic causes of stroke in AF

- A proportion (~25%) of strokes in AF occur from causes other than thromboembolism:[1,2]
  - Thromboembolism from heart chambers other than the left atrium
  - Atherosclerotic plaques in vessels (e.g. proximal aorta)
  - Underlying cerebrovascular disease

CHA_2DS_2-VASc SCORE

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

Approach to thromboprophylaxis in AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

AF = atrial fibrillation; CHA_2DS_2-VASc = cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

www.escardio.org/guidelines

European Heart Journal (2010) 31, 2369-2429

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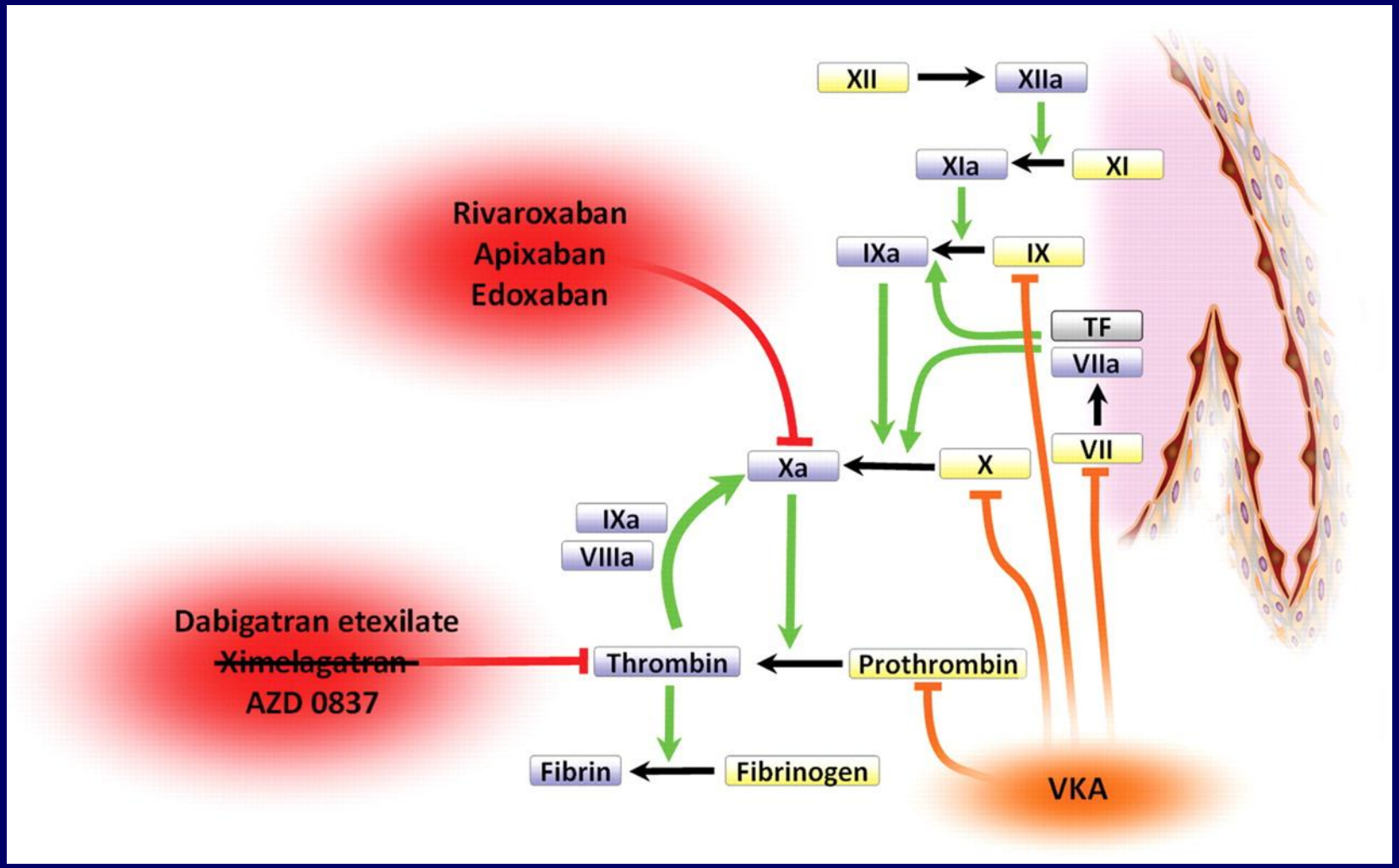
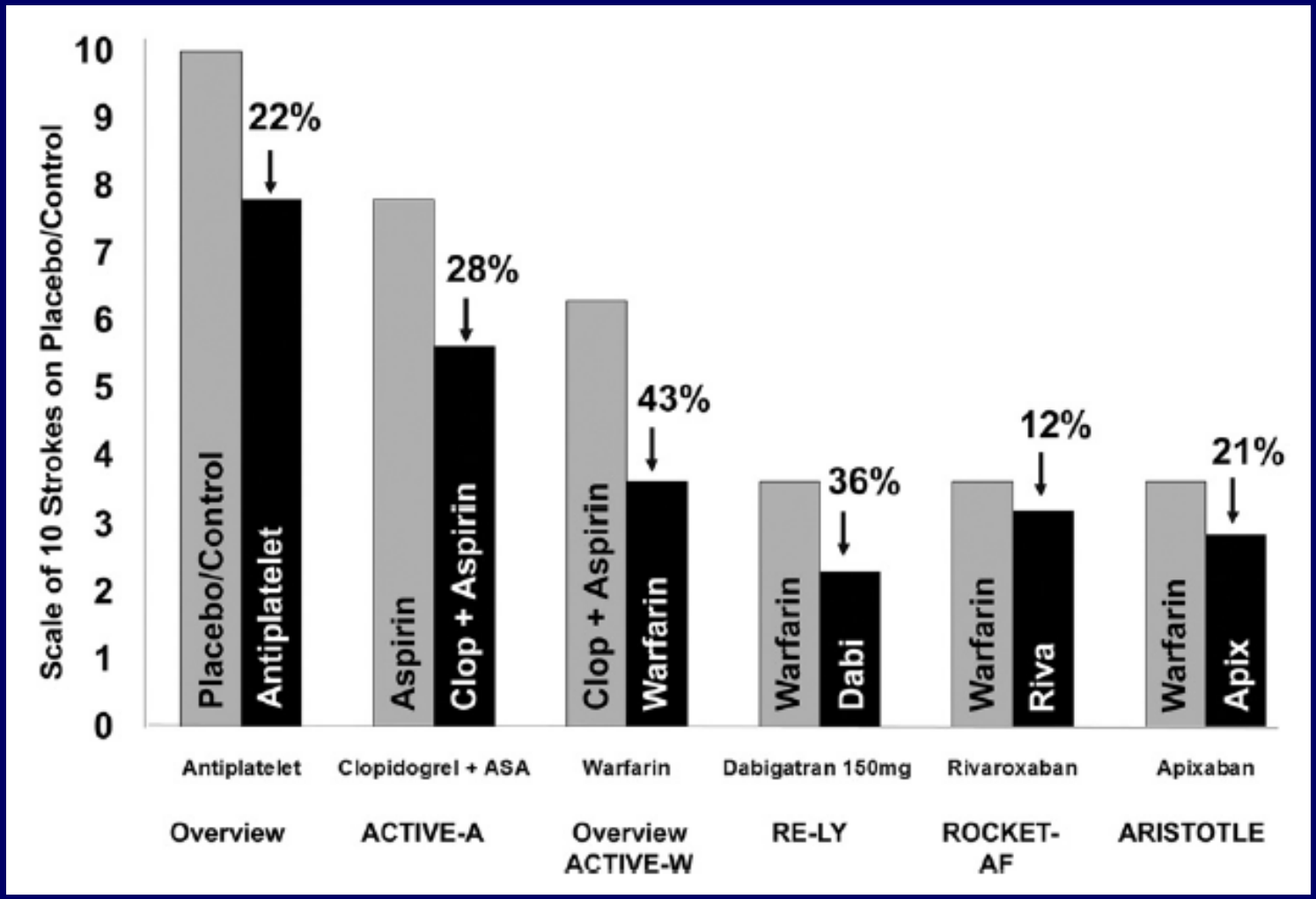
Point of action of novel oral anticoagulants in the coagulation cascade



Steffel J , Braunwald E Eur Heart J 2011;32:1968-1976

European Heart Journal

The evolution of antithrombotic treatment for stroke prevention in AF



CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Should Newer Oral Anticoagulants Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation and Risk Factors for Stroke or Thromboembolism?

New Oral Anticoagulants Should Not Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation

Jack Ansell, MD

Circulation 2012;125:165-70

Rates of stroke/embolism at different levels of warfarin therapeutic control

RELY study

Table 1.

Rates of Stroke and Systemic Embolism of Dabigatran Compared With Different Levels of Warfarin Therapeutic Control as Determined by Time in Therapeutic INR Range. RE-LY Rates of Stroke and Systemic Embolism per 100 Person-Years (Hazard Ratio, 95% Confidence Interval vs Warfarin)[8]

INR Time in Therapeutic Range, %	Dabigatran 110 mg Twice a Day	Dabigatran 150 mg Twice a Day	Warfarin
<57.1	1.91	1.10	1.92
	1.00 (0.68-1.45)	0.57 (0.37-0.88)	
57.1-65.5	1.67	1.04	2.06
	0.81 (0.56-1.17)	0.50 (0.33-0.77)	
65.5-72.6	1.34	1.04	1.51
	0.89 (0.58-1.36)	0.69 (0.44-1.09)	
>72.6	1.23	1.27	1.34
	0.92 (0.59-1.45)	0.95 (0.61-1.48)	

- INR indicates international normalized ratio; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy.

ROCKET-AF study

Table 2.

Rates of Stroke and Systemic Embolism of Rivaroxaban Compared With Different Levels of Warfarin Therapeutic Control as Determined by Time in Therapeutic INR Range. ROCKET-AF Rates of Stroke and Systemic Embolism per 100 Person-Years (Hazard Ratio, 95% Confidence Interval vs Warfarin)[3]

INR Time in Therapeutic Range, %	Rivaroxaban	Warfarin
0-50.6	1.8	2.5
	0.71 (0.48-1.03)	
50.7-58.5	1.9	2.2
	0.83 (0.62-1.29)	
58.6-65.7	1.9	2.1
	0.92 (0.62-1.28)	
65.7-100	1.3	1.8
	0.77 (0.49-1.12)	

- INR indicates international normalized ratio; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

Disadvantages of New Oral Anticoagulants (1)

Short half-life

Potential for increased risk of stroke or systemic embolism with poor drug adherence

No routine coagulation monitoring required

Potential for increased risk of stroke or systemic embolism with poor drug adherence

Disadvantages of New Oral Anticoagulants (2)

No coagulation assay available to precisely measure anticoagulation effect

- Cannot titrate dose
- Cannot assess cause for failure of therapy (poor adherence vs failure)
- Cannot easily assess degree of coagulation inhibition in emergent situations such as urgent surgery or life-threatening bleeding

No antidote or well-established procedure for reversing anticoagulation in emergent situations

Cost

Other potential problems…

RELY study

Drop-outs rate 21% Dabigatran vs 17% Warfarin

Significant increase in dyspepsia (12% vs 6%)

Significant increase in major gastrointestinal bleeding compared with warfarin (Dabigatran 150mg)

	RELY (D150)	ROCKET AF	AVERROES	ARISTOTLE
Major bleeding	**3.11% vs 3.36%/yr (p=0.31)**	**3.60% vs 3.46%/yr (p=0.576)**	**1.4% vs 1.2%/yr (p=0.57)**	**2.13% vs 3.09%/yr (p<0.001)**
Intracranial hemorrhage	**0.30% vs 0.74%/yr (p<0.001)**	**0.49% vs 0.74%/yr (0.019)**	**0.4% vs 0.4%/yr (p=0.35)**	**0.33% vs 0.80%/yr (p<0.001)**
Clinically relevant nonmajor bleeding	**NA**	**11.80% vs 11.37%/yr (p=0.345)**	**3.1% vs 2.7%/yr (p=0.35)**	**4.07% vs 6.01%/yr (p<0.001)**