ATRIAL FIBRILLATION AND STROKE PREVENTION – WARFARIN IS NO MORE AN OPTION

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Introduction: Atrial fibrillation (AF) [1] is a tachy arrhythmia arising above the ventricular tissue and is characterized by bizarre atrial activation with consequent deteriotation of mechanical function ie atrial contraction. Estimated prevalence of atrial fibrillation is approximately 1% which increases with age to 6% by the age of 65 and to 10% at the age of 80+. [2,3,4.] Management of atrial fibrillation involves three key areas, namely control of the rate and the rhythm and the prevention of thromboembolic manifestations.

Atrial fibrillation and stroke: Patients with AF have higher risk of embolic stroke, heart failure, cognitive decline, reduced quality of life and higher mortality. Stroke risk is increased five fold in patients with AF and 25% of all the stroke in the elderly are due to AF [5,6,7]. AF related stroke are severe and cause more death [8,9,10]. Anti thrombotics and anti platelet drugs are the mainstay for prevention of systemic thromboembolism.

Treatment options for Stroke prevention in patients with AF: Among the various options, Aspirin, though it is convenient to use but provides insufficient protection,for stroke prevention in high-risk patients

Vitamin K antagonists especially Warfarin have greater efficacy but a range of limitations make them inferior agents to use because of the following reasons:

- Narrow therapeutic window
- Variable and unpredictable pharmacokinetics and pharmaco dynamics
- Wide variety of drug–drug and drug–food interactions
- Need for regular anticoagulation monitoring and dose adjustments
- Slow onset and offset of action.

The most feared complication of antithrombotic therapy is intra cerebral haemorrhage. The Vitamin K antagonist (VKAs) warfarin is used in only half of eligible patients with Atrial Fibrillation. Under use of warfarin is greatest in elderly patients who are at the highest risk of stroke. They have a very narrow therapeutic window. The contraindications that make patients unsuitable for VKAs are found most frequently in elderly patients who are often at the greatest risk of stroke [11,12 ,13,14.] Failure to prescribe warfarin for eligible patients is a pervasive problem, despite available guidelines for its use in non valvular AF who have moderate to severe risk of stroke. [15,16]. Only 65% of patients with heart failure and AF were prescribed warfarin at the time of discharge.[17, 18]. Thus a large number of patients with AF are not being prescribed or are refusing to take it or are stopping it on their own. Hence the search for newer ideal anti coagulants was on.

Ideal anticoagulant should be effective with minimal complications/side effects,should be convenient to administer (ie: oral for outpatients). It should be rapidly absorbed and should have fast on and offset action, predictable pharmacokinetics with no interactions with food or drugs and no need to monitor.

New anticoagulants are challenging the predominance of Vitamin K antagonist especially warfarin for stroke prophylaxis in patients with AF. Since 2007, three large trials of novel anticoagulants compared to VKA have been completed with a combined sample size of approximately 50,000 subjects:

Re-LY, with approximately 18,000 subjects and the new director factorII (thrombin) antagonist DABIGATRON.[19].

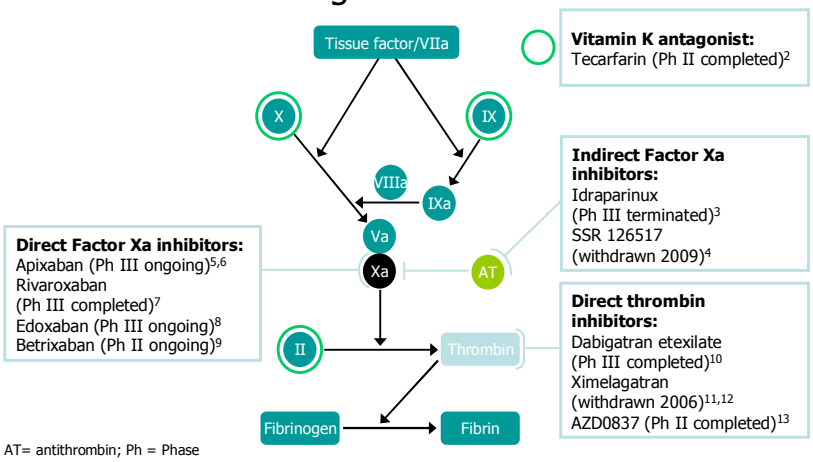
ROCKET AF with approximately 14000 subjects and the new factor X inhibitor. RIVAROXABAN [20,21].

ARISTOTLE with approximately 14,000 subjects and the new factor X inhibitor APIXABON [22].

Mechanical devices like left atrial appendage occlusive devices (LAA) are increasingly used in elderly patients with AF with a history of falls or previous history of bleeding or pregnant women and / or noncompliant patients.

Conclusion: The newer novel anticoagulants and the mechanical devices should be considered as an alternative replacement to VKAespecially the warfarin. The time to say “good bye” to warfarin has come.

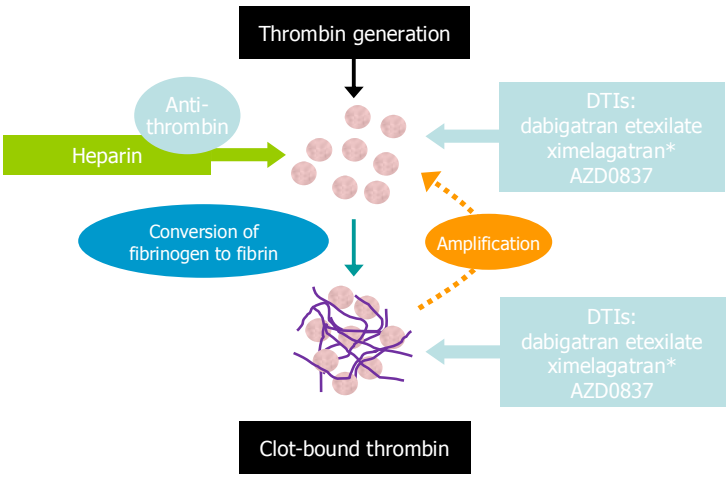
Targets for novel antithrombotic agents in the coagulation cascade[1]



AT= antithrombin; Ph = Phase

1. Adapted from Turpie AG. Eur Heart J 2008;29:155–65; **2.** Ellis DJ et al. Circulation 2009; 120:1029–35; **3.** Bousser MG et al. Lancet 2008;371:315–21; **4.** NCT00580216; available at www.ClinicalTrials.gov; accessed Sept 09; **5.** Lopes RD et al. Am Heart J 2010;159:331–9; **6.** Eikelboom JW et al. Am Heart J 2010;159:348–53; **7.** ROCKET-AF Study Investigators. Am Heart J 2010; 159:340–47; **8.** NCT00781391; available at www.ClinicalTrials.gov; accessed Sept 09; **9.** NCT00742859; available at www.ClinicalTrials.gov; accessed Sept 09; **10.** Connolly SJ et al. N Engl J Med 2009;361:1139–51; **11.** Olsson SB et al. Lancet 2003;362:1691–8; **12.** Albers GW et al. JAMA 2005;293:690–8; **13.** Lip GY et al. Eur Heart J 2009;30:2897–907

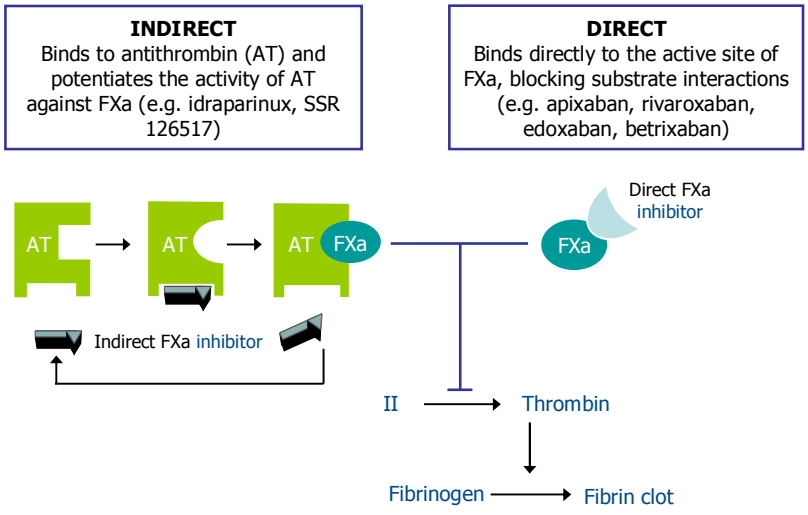
Direct thrombin inhibitors (DTIs) block both circulating and clot-bound thrombin



*Withdrawn from the market in 2006

Adapted from Eikelboom J et al. J Am Coll Cardiol 2003;41:70S–8S

Direct and indirect factor Xa (FXa) inhibition



Adapted from Turpie AG et al. N Engl J Med 2001;344:619–25

New and Emerging Anticoagulants

- **Anti – Xa : direct**
  - **Rivaroxaban (oral)**
  - **Apixaban (oral)**
  - Betrixiban (oral)
  - Edoxaban (oral)
  - Otamixaban (parenteral)
  - LY – 517717 (oral)
  - DU – 176B (oral)
  - DX – 9065a (parenteral)
  - PRT054021 (oral)

- **Anti – Xa : indirect**
  - **Idraparinux biotinylated (parenteral)**

- **Anti – IIa**
  - **Dabigatran (oral)**
  - Odiparcil (oral)
  - Flovagatran (parenteral)
  - Pegmusirudin (parenteral)
  - Peg Hirudin
  - Desiruidin

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