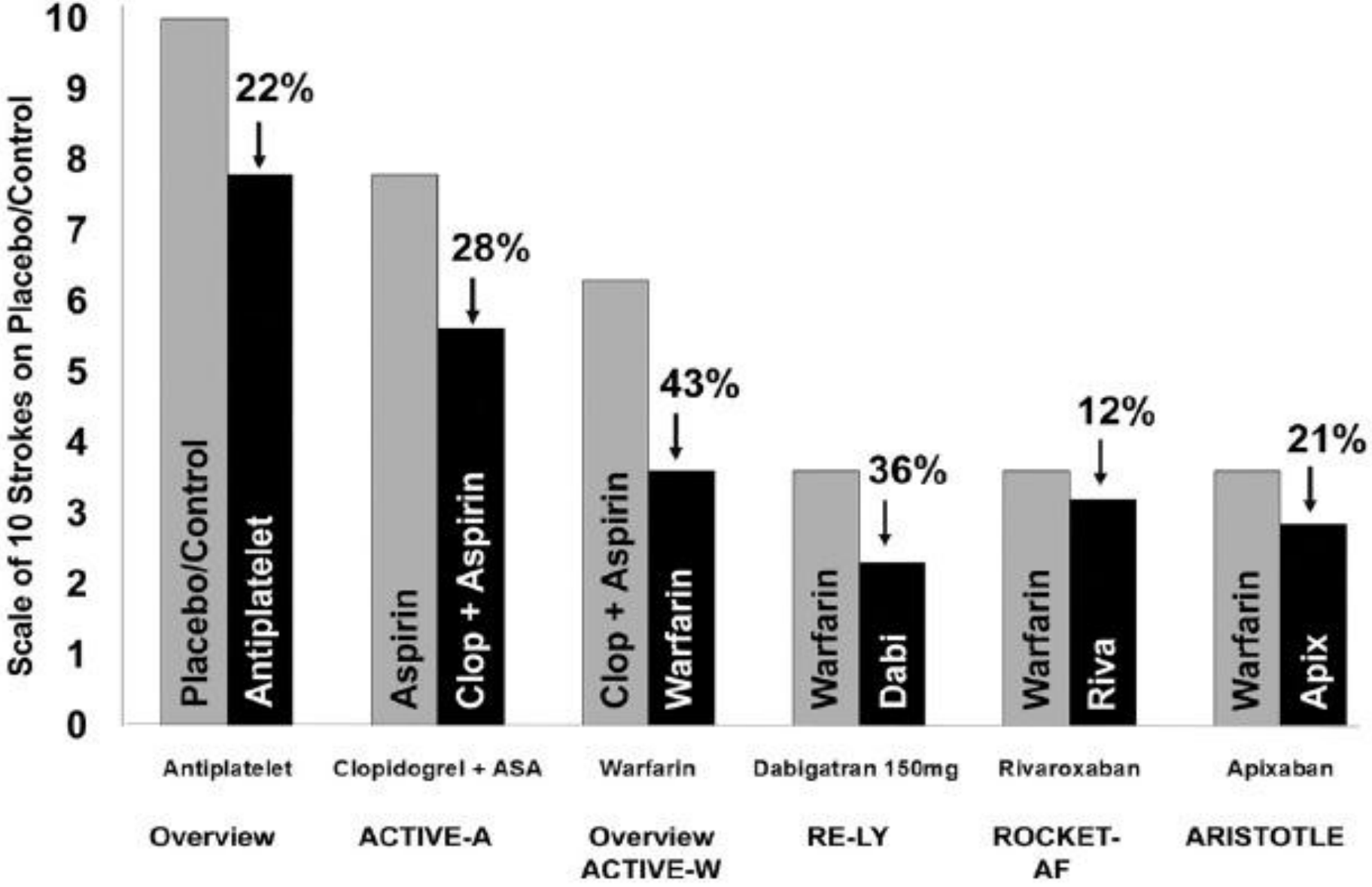
Head to head comparison

Dr. Anup Kumar Saha
Associate Professor
Department of Medicine
Sir Salimullah Medical College.

TRIALS

RE-LY Trial:

- The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial.
- Non inferiority randomized trial with open-label warfarin and dabigatran.
- Included 18 113 patients with AF and at least 1 risk factor for stroke.
- Dabigatran is safe and effective compared with warfarin.



The Figure shows the effect of
various antithrombotic therapies on stroke, with the use of an
arbitrary scale of 10 for no therapy.

Table 2. Results of Large Randomized Clinical Trials of New Anticoagulants vs Warfarin

	Novel Drug and Dose	Clinical Events		Hazard Ratio (95% CI)	*P* (Superiori
		Novel Agent	Warfarin		
		Stroke or Systemic Embolism, %/y			
RE-LY	Dabigatran 110 mg twice a day	1.53	1.69	0.91 (0.74–1.11)	0.34
	Dabigatran 150 mg twice a day	1.11	1.69	0.66 (0.53–0.82)	<0.001
ROCKET-AF	Rivaroxaban 20 mg every day	2.12	2.42	0.88 (0.75–1.03)	0.12
ARISTOTLE	Apixaban 5 mg twice a day	1.27	1.60	0.79 (0.66–0.95)	0.01
		Hemorrhagic Stroke, %/y			
RE-LY	Dabigatran 110 mg twice a day	0.12	0.38	0.31 (0.17–0.56)	<0.001
	Dabigatran 150 mg twice a day	0.10	0.38	0.26 (0.14–0.49)	<0.001
ROCKET-AF*	Rivaroxaban 20 mg every day	0.26	0.44	0.59 (0.37–0.93)	0.02
ARISTOTLE	Apixaban 5 mg twice a day	0.24	0.47	0.51 (0.35–0.75)	<0.001
		Ischemic or Uncertain Stroke, %/y			
RE-LY	Dabigatran 110 mg twice a day	1.34	1.20	1.11 (0.89–1.40)	0.35
	Dabigatran 150 mg twice a day	0.92	1.20	0.76 (0.60–0.98)	0.03
ROCKET-AF*	Rivaroxaban 20 mg every day	1.34	1.42	0.94 (0.75, 1.17)	0.58
ARISTOTLE	Apixaban 105 mg twice a day	0.97	1.05	0.92 (0.74–1.13)	0.42

ROCKET-AF*	Rivaroxaban 20 mg every day	1.34	1.42	0.94 (0.75, 1.17)	0.58
ARISTOTLE	Apixaban 105 mg twice a day	0.97	1.05	0.92 (0.74–1.13)	0.42
		Major Bleeding, %/y			
RE-LY	Dabigatran 110 mg twice a day	2.71	3.36	0.80 (0.69–0.93)	0.003
	Dabigatran 150 mg twice a day	3.11	3.36	0.93 (0.81–1.07)	0.31
ROCKET-AF*	Rivaroxaban 20 mg every day	3.60	3.45	1.04 (0.90–1.20)	0.58
ARISTOTLE*	Apixaban 5 mg twice a day	2.13	3.09	0.69 (0.60–0.80)	<0.001
		Death, %/y			
RE-LY	Dabigatran 110 mg twice a day	3.75	4.13	0.91 (0.80–1.03)	0.13
	Dabigatran 150 mg twice a day	3.64	4.13	0.88 (0.77–1.00)	0.051
ROCKET-AF	Rivaroxaban 20 mg every day	4.5	4.9	0.92 (0.82–1.03)	0.15
ARISTOTLE	Apixaban 5 mg twice a day	3.52	3.94	0.89 (0.80–0.998)	0.047

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulant Therapy; 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; and ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation.

*On-treatment population.

- Warfarin was used with an INR target of 2.0 to 3.0, which was achieved 64% of the time in the trial.
- Two doses of dabigatran (110 and 150 mg twice daily) were studied.
- Dabigatran 150 mg was superior to warfarin in reducing the incidence of stroke (including hemorrhagic) and systemic embolism by 34% (*P<0.001).*

- Dabigatran 110 mg was non inferior to warfarin in preventing stroke and systemic embolism.

- 20% relative risk reduction in major bleeding compared with warfarin (*P<0.003).*

ROCKET-AF Trial:

- *The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation* .
- Double-blind, randomized comparison of Rivaroxaban 20 mg once daily (with dose adjustment for renal function) versus dose-adjusted warfarin .

- 12% relative risk reduction in the occurrence of stroke and systemic embolism in AF patients treated with Rivaroxaban that did not reach statistical significance but was clearly non inferior to warfarin.
- There were significant reductions in intracranial hemorrhage, as well as in bleeding causing death.

AVERROES Trial:

- *The Apixaban Versus Acetylsalicylic Acid to Prevent Strokes*
- This large double blind randomized study compared the efficacy of apixaban 5 mg twice daily with aspirin (81–325 mg once daily)
- For stroke and systemic embolism prevention in 5599 AF patients;
- Who were considered unsuitable for vitamin K antagonist treatment

- The trial was stopped early on recommendation by the Data and Safety Monitoring Board.
- Because of clear benefits in regard to stroke reduction favoring apixaban (hazard ratio, 0.46; 95% confidence interval, 0.33–0.64; *P<0.001).*

- Strikingly, Apixaban was associated with rates of major bleeding similar to those observed with aspirin.
- Apixaban was better tolerated than aspirin, with significantly fewer study drug discontinuations.

ARISTOTLE trial:

- *The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*.
- This was a large randomized, double-blind trial.

- Compared with warfarin, apixaban reduced stroke and systemic embolism by 21% (*P<0.01), resulted in 31% less bleeding (P<0.001),*
- *Resulted* in 11% lower mortality (*P<0.047).*
- *Apixaban was better* tolerated than warfarin,
- With fewer drug discontinuations.

ENGAGE AF-TIMI 48 Trial:

This is a double blind randomized trial

This compares endoxaban and warfarin

This included 20,000 patients with AF

Result is expected to be published this year.

Efficacy Outcomes

Efficacy Outcomes

- All 3 new anticoagulants are at least as good as warfarin at preventing stroke, and because warfarin itself is very effective, the benefit compared with no therapy could not be measured.
- Dabigatran 150mg twice daily and Apixaban 5 mg twice daily are more effective than warfarin in terms of preventing stroke.
- All 3 resulted in an 10% reduction in mortality, although this reached statistical significance only for Apixaban.

Safety Outcomes

- The rate of hemorrhagic stroke was reduced by 40% to 70% and that of intracranial hemorrhage by 50% with all 3 of the agents,
- Both lower-dose dabigatran and apixaban resulted in important reductions in major bleeding.
- All 3 new anticoagulants result in an 10% reduction in mortality,

Convenience

The new oral anticoagulants are far more convenient than warfarin because

- Predictable pharmacodynamic effects
- Good efficacy and safety profiles without anticoagulation monitoring.
- Avoid frequent dose adjustment that may contribute to dosing errors.
- Rapid onset of action and relatively short half-life periods.

Lack of Specific Antidotes

- The safety of the new drugs has been challenged because there is no reversal agent.

- But the reversal agents are little required because: 1. they have short half life
  2. they cause less bleeding,

Thank you.