Introduction:

NOAC or **N**ovel **O**ral **A**nti-**C**oagulants also **N**on-Vit K **O**ral **A**nti-**C**oagulants are newer generation oral anti-coagulating agents, which do not act upon the pathway of anti-coagulation as regards to conventional oral anti-coagulants viz. Warfarin.

Mechanism of action:

1. Direct Thrombin Inhibitor: Dabigatran.
2. Factor Xa Inhibitor: Apixaban, Rivaroxaban, Edoxaban.

Uses:

1. Stroke prevention in AF.
2. Prevention of Venous Thromboembolism (VTE) after elective Hip/Knee replacement surgery.
3. Treatment and prophylaxis for DVT.
4. Treatment and prophylaxis of Pulmonary Embolus.
5. Prevention of recurrent ischemia in stable patient of ACS.

*all are not US-FDA approved uses of NOAC.

Side effects:

1. Bleeding
2. Severe headache
3. Dizziness/fainting
4. Tiredness/weakness
5. Heartburn/nausea/vomiting
6. Allergic reactions

Why anti-coagulation in AF?

AF or Atrial Fibrillation is a condition where there is no proper contraction of Atriums, only fibrillary movements. In such condition there is stasis of blood in the Atriums which can lead to clot formation. This clot if passes through ventricles, which have normal contractions, to the lungs via Right ventricle or whole body via Left Ventricle can lead to serious embolic events which might even lead to death if not urgently treated.

The chief hazard of AF is stroke, the risk of which is increased 4-5-fold. Because of its high prevalence in advanced age, AF assumes great importance as a risk factor for stroke and by the ninth decade becomes a dominant factor. The attributable risk for stroke associated with AF increases steeply from 1.5% at age 50-59 years to 23.5% at age 80-89 years. AF is associated with a doubling of mortality in both sexes, which is decreased to 1.5-1.9-fold after adjusting for associated cardiovascular conditions. Decreased survival associated with AF occurs across a wide range of ages.1

Race/ethnicity influences the risk of stroke in patients with AF. In whites, blacks, Hispanics, and Asians who are treated with warfarin, the ischemic stroke rates per 1000 person-years' follow-up are 15.9, 27.1, 15.1, and 13.4, respectively , while the equivalent rates for subjects not using warfarin are 20.3, 29.4, 21.3, and 20.6 strokes per 1000 person-years, respectively.2

Healey *et al*.3 showed that rates of stroke occurrence within a year of presenting with AF at a hospital emergency department according to the countries were as follows: North America, Western Europe, or Australia (2%), South America (3%), Eastern Europe (4%), Southeast Asia (7%), China (7%), Africa (8%), and India (0.8%). The incidence of all-causes death within 1 year after presenting with AF also varies widely between these regions from 9% to 20%.

Assessing Stroke in AF : *CHA2DS2-VASc score*

CHA2DS2-VASc is the most recent scoring system used for estimating the risk of stroke in AF patients and determining whether or not treatment with anti-coagulation or anti-platelets is required.

	Condition	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A2	Age≥75years	2
D	Diabetes Mellitus	1
S2	Prior Stroke/TIA/Thromboembolism	2
V	Vascular diseases (e.g. PAD, MI, Aortic plaque)	1
A	Age 65-74years	1
Sc	Sex category (i.e. female sex)	1

Score	Risk	Anti-coagulation Therapy

0 (male) or 1 (feale)	Low	Not required
1(male)	Moderate	Should be considered
2 or greater	High	Recommended

The European Society of Cardiology (ESC)4, and National Institute for Health and Care Excellence (NICE)5 guidelines recommend that if the patient has a CHA2DS2-VASc score of 2 and above, oral anticoagulation therapy (OAC) with a Vitamin K Antagonist (VKA, e.g. warfarin with target INR of 2-3) or one of the non-VKA oral anticoagulant drugs (NOACs, e.g. dabigatran, rivaroxaban, edoxaban, or apixaban) is recommended.

Bleeding Risk Assessment:[6]

The approach to thromboprophylaxis in AF requires not only assessment of stroke risk, but also the risk of bleeding. A new bleeding scoring system has been proposed with the acronym HAS-BLED (uncontrolled Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly> 65 years, Drugs/alcohol concomitantly). One point is given for each risk factor with a maximums score of 9. A score of ≥ 3 suggests a high risk of bleeding that merits some caution and/or regular clinical review of the patient. The HAS-BLED score is a potential practical tool in clinical decision making, as recommended in recent guidelines. After all, the HAS-BLED score is simple to use, and makes clinicians think about addressing any correctable bleeding risk factors (e.g. uncontrolled hypertension, co-administration of NSAIDs or aspirin, etc.).

	Condition	Points
H	HTN (uncontrolled, >160mmHg systolic)	1
A	Abnormal Renal function Abnormal Liver function	1 1
S	Prior history of Stroke	1
B	Bleeding- prior major bleeding or predisposition to bleeding	1
L	Labile INR- unstable/high INR, time in therapeutic range <60%	1
E	Elderly- age>65years	1
D	Prior Alcohol/Drug history(≥8drinks/week) Medication usage predisposing to bleeding- anti-platelets, NSAIDS	1 1

Is there a need to think beyond WARFARIN in AF?

Warfarin first came into commercial use in 1948 as a rat poison. In 1954 it was approved for medical use in the United States. Since then it has been the ‘Man Friday’ for physicians in

stroke prevention in AF and others. Warfarin is the most widely used anticoagulant in the world.

Use of Warfarin:

1. ***Pros:***
    - Low cost.
    - Easy availability.
2. ***Cons:***
    - **Major and fatal bleeding**: According to a meta-analysis of 33 studies, it was seen that the rate of major and fatal bleeding events were 7.2 and 1.3 per 100 patient-years.7
    - **Narrow therapeutic index**: A recent analysis of 6454 patients with atrial fibrillation taking warfarin showed that for almost 50% of the time, the INR was outside the target range of 2–3.8
    - **Different dosing**: Individual dosage requirements vary widely between and within individuals.
    - **Frequent monitoring**: because of narrow therapeutic index and different dosing requirements PT/INR has to be frequently monitored.
    - **Hidden Costs**: Though the medicine is cheap but the indirect cost of frequent monitoring of PT/INR and also cost of hospital admission due to major bleedings, etc.

Role of NOAC in non-valvular AF:

US-FDA has approved four NOACs namely Dabigatran, Rivaroxaban, Apixaban and Edoxaban for use in non-valvular AF for stroke prevention. As compared to Warfarin, NOACs have fixed drug regimen, lesser food-drug and drug-drug interaction and also do not require frequent anti-coagulation monitoring. Dabigatran was approved in 2010 for a dose of 150mg BD, Rivaroxaban in 2011 for dose of 20mg OD, Apixaban in 2012 for a dose of 5mg BD and Edoxaban in 2015 for a dose of 60mg OD.

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	79-100%	3-7%	66% without food, 100% with food	50%	62%
Time for peak effect	1.5-3days	2-3hr	2-4hr	3-4hr	1-2hr
Plasma t1/2	20-60hr	12-17hr	5-13hr	8-14hr	5-11hr
Clearance (renal/non-renal)	92/8	80/20	27/73	50/50	35/65

TUG of WAR (NOAC Vs WARFARIN):

Ever since the approval of NOACs debate has been going on regarding the better choice of drug for prevention of stroke in AF. Various trials were undertaken for the same. Of the various trials, four are worth mentioning.

1. RELY9: The Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial compared dabigatran150 mg (D150) and dabigatran110 mg (D110) BID with Warfarin in 18113 atrial fibrillation patients. Those with prosthetic heart valves, significant mitral stenosis and valvular heart disease (VHD) requiring intervention were excluded. Others with VHD were included.
2. ROCKET-AF10: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a double blinded study where 14264 patients, with non-valvular AF who were at increased risk for stroke, to receive either Rivaroxaban 20mg OD or dose adjusted Warfarin.
3. ARISTOTLE11: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial

Fibrillation (ARISTOTLE) was also a randomized double-blinded trial conducted in 18201

patients divided randomly into two groups. One group was given Apixaban 5mg BD and another group received dose adjusted Warfarin.

1. ENGAGE AF TIMI-4812 : Effective Anticoagulation with Factor Xa Next Generation in Atrial

Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) was a randomized, double-blind, double-dummy trial comparing two once-daily regimens (30mg and 60mg) of Edoxaban with Warfarin in 21,105 patients with moderate to high-risk atrial fibrillation.

	RELY	ROCKET AF	ARISTOTLE	ENGAGE AF TIMI48
No. of patients	18113	14264	18201	21105
Follow-up	2 yr	1.9 yr	1.8 yr	2.8 yr

Groups	Dose adjusted warfarin(W) vs Dabigatran 110mg(D110) BD and 150mg(D150)BD	Dose adjusted Warfarin(W) Vs Rivaroxaban 20mg(R20) OD	Dose adjusted Warfarin (W) Vs Apixaban 5mg(A5) BD	Dose adjusted warfarin (W) Vs Edoxaban 30mg(E30) OD and 60mg(E60)OD
Study design	Randomised, open label	Randomised, double blinded	Randomised, double blinded	Randomised, double blinded

The results of these 4 studies are presented in the following table:

		RELY		ROCKET AF		ARISTOTLE		ENGAGE AF		TIMI48
	W	D110	D150	W	R20	W	A5	W	E30	E60
	n=6022	n=6015	n=6076	n=7133	n=7131	n=9081	n=9120	n=7045	n=7034	n=7035
Stroke/Systemic embolism	1.71	1.54	1.11	2.4	2.1	1.6	1.27	1.5	1.61	1.18
		p<0.001	p<0.001		p<0.001		p<0.001		p=0.005	p<0.001
Ischemic Stroke	1.21	1.34	0.92	1.42	1.34	1.05	0.97	1.25	1.77	1.25
		p=0.35	p=0.03		p=0.581		p=0.42		p<0.001	p=0.97
Hemorhagic Stroke	0.38	0.12	0.1	0.44	0.26	0.47	0.24	0.47	0.16	0.26
		p<0.001	p<0.001		p=0.24		p<0.001		p<0.001	p<0.001
Major Bleeding	3.57	2.87	3.32	3.4	3.6	3.09	2.13	3.43	1.61	2.75
		p=0.003	p=0.31		p=0.58		p<0.001		p<0.001	p<0.001
ICH	0.76	0.23	0.32	0.7	0.5	0.8	0.33	0.85	0.26	0.36
		p<0.001	p<0.001		p=0.002		p<0.001		p<0.001	p<0.001
GI Bleed	1.07	1.15	1.56	2.2	3.2	0.86	0.76	1.23	0.82	1.51
		p=0.52	p<0.001		p<0.001		p=0.37		p<0.001	p=0.03
MI	0.64	0.82	0.81	1.1	0.9	0.61	o.53	0.75	0.7	0.89
		p=0.009	p=0.12		p=0.12		p=0.37		p=0.6	p=0.13
All cause Mortality	4.13	3.75	3.64	2.2	1.9	3.94	3.52	4.35	3.8	3.99
		p=0.13	p=0.051		p=0.007		p=0.047		p=0.006	p=0.08

Indian Perspective:[13,14]

In our country, there is virtually no data on AF, most of the data that has been derived is from international studies with an Indian cohort. There is indeed a dearth of data on epidemiologic outcomes in patients of rheumatic AF in the country leading to inconsistent practice patterns as regards medical therapy, especially oral anticoagulation. This exposes these patients at a higher risk of thromboembolic and sometimes bleeding diathesis.

In a population based study of 984 healthy subjects residing in a Himalayan village15, the prevalence of AF of 0.1% was reported which was quite low as compared to the western population but this study included young, healthy participants (only 6% > 65 years of age), limitation being all were from only one village in the Himalayas and were subjected to only a one time ECG.

The incidence, prevalence, risk factors and economic burden of AF in Indians are different from those in Western population. Indian patients of AF are about a decade younger and have female preponderance, which could be attributed to Rheumatic valvular disease. More proportion of Indian patients has persistent/permanent AF thus representing a higher stroke risk. Data from the IHRS-AF registry and the Indian subset REALISE-AF and RELY-AF studies also reaffirmed these findings.

The situation becomes grimmer when we observe that the time spent in the therapeutic range for oral anticoagulation is significantly lower in countries outside North America and Western Europe. As shown in the ROCKET AF trial among closely monitored patients in the warfarin arm, a substantial proportion of participants from different geographical regions had sub-therapeutic anticoagulation (INR <2 for >25% of the time): 44% in India and 27% in Latin America, about 37% in East Asia and 35% in Eastern Europe.

Data from the IHRS-AF registry and the Indian subset of REALISE

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NOACs in valvular AF ?

NOACs have been coming up as the first line of treatment for stroke prevention in non-valvular AF on the basis of the different trials done throughout the globe, but their use in

valvular AF is in controversial state. There is no uniform definition of 'Valvular AF' in different guideline. Also the exclusion criteria of the different trials are also not uniform. In ROCKET-AF trial prosthetic heart valve or haemodynamically significant mitral stenosis were excluded, whereas in the ENGAGE-AF TIMI 48 trial, moderate or severe mitral stenosis and a mechanical heart valve were excluded whilst bioprosthetic heart valves and/or valve repair were allowed. As a result, uncertainty persists among practicing physicians whether a given patient with valvular heart disease is eligible for NOAC treatment. As a result, patients with valvular disorders other than the ones mentioned above, including frequently encountered entities such as aortic stenosis or mild-to-moderate mitral regurgitation, were often denied NOACs based on the perception that they were suffering from valvular AF.16 The point to note here is that 20-25% of patients included in RELY, ARISTOTLE and ROCKET-AF had AS, AR, MR, etc. The only two things excluded were severe MS and bioprosthetic heart valves.

In RE-ALIGN17 trial Dabigatran was used in mechanical heart valves. But this trial had to be prematurely stopped due to excess of thromboembolic and bleeding events among patients in the dabigatran group. But the point to note is that the dose of dabigatran that was used in this trial was very high which might be the reason for the unfavorable outcome.

Conclusion:

Warfarin used to be the only option for oral anticoagulation for prevention of stroke in AF patients but now NOACs have come up as a better alternative. All the studies clearly show NOACs to be better than Warfarin in terms of stroke prevention and avoiding fatal outcomes. The only hurdle till date for the generalized use of NOACs was their high costs, due to their respective patents. But recently Dabigatran has gone off-patent so its price is likely to go down considerably, which will make it the most sought after oral anti-coagulant for stroke prevention in AF patients.

References:

1. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N–9N. pmid:9809895
2. Retrieved from http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179687
3. Retrieved from http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30968-0/fulltext
4. "2016 ESC Guidelines for the management of atrial fibrillation developed in

collaboration with EACTS". European Heart Journal. 37(38):2893-2962. doi: 10.1093/eurheartj/ehw210
5. Retrieved from https://www.nice.org.uk/guidance/cg180
6. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2011.04302.x/full
7. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med. 2003;139(11):893–900. [PubMed]
8. Boulanger L, Kim J, Friedman M, Hauch O, Foster T, Menzin J. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. Int J Clin Pract. 2006;60(3):258–64. [PubMed]
9. Retrieved from https://doi.org/10.1161/CIRCULATIONAHA.115.020950
10. N Engl J Med 2011; 365:883-891 DOI: 10.1056/NEJMoa1009638
11. N Engl J Med 2011; 365:981-992 DOI: 10.1056/NEJMoa1107039
12. N Engl J Med 2013; 369:2093-2104 DOI: 10.1056/NEJMoa1310907
13. http://www.j-pcs.org/article.asp?issn=2395-5414;year=2015;volume=1;issue=3;spage=230;epage=232;aulast=Bohra
14. https://www.researchgate.net/publication/316855093_Atrial_Fibrillation_in_India_Is_it_a_Tide_Rising_or_a_Tsunami
15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3861218/
16. Retrieved from https://www.researchgate.net/publication/283785355_Non-Vitamin_K_oral_anticoagulants_in_'valvular'_atrial_fibrillation_A_call_for_action
17. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23991661

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