NEWER DEVELOPMENTS IN ORAL ANTICOAGULANTS

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INTRODUCTION:
For decades, oral Vitamin K Antagonists (VKA) have ruled the roost as anticoagulants. A narrow therapeutic range, drug-drug and food interactions and need of monitoring prothrombin time (INR), impair their effectiveness and safety. The newer anticoagulants developed as alternatives act through direct thrombin inhibition (Dabigatran) and Factor Xa inhibition (Rivaroxaban, Apixaban, Betrixaban and Edoxaban). Current evidence is available through phase III trials of Dabigatron (RELY) and Apixaban (ARISTOTLE). Newer developments are taking place in other agents. Majority evidence is also in prevention of embolic events in atrial fibrillation (AF). These agents have a potential to replace Warfarin (VKA) class of drugs in other indications too. Large experience, evidence and lower cost still favour use of VKA. With newer advances and developments, will the newer oral anticoagulants replace the established VKA and if they do, how will these fit into the therapeutic armamentarium of practicing physicians is a clinical curiosity.2

HISTORY & BACKGROUND:
Coumadins (VKA) were developed 60 years ago and have been the sole anticoagulants for all these decades. Their clinical use has preceded the understanding of their mechanism of action. It was discovered by chance from extracts of vegetable matter (spoiled sweet clover). More research was then focused to extract anticoagulants from insects & snake venoms. Thrombin inhibitors were isolated, purified and also synthesized by recombinant techniques. Further advance led to the new anticoagulants that are small molecules designed specifically to block coagulation enzymes and modulating the coagulation process at almost every step. Initial advances took place in development of parenteral anticoagulants (LMWH, Bivaluridin and Fondaparinux). These agents established themselves quickly as alternatives for UFH. Thus the pressing need was to develop oral anticoagulants which could replace Coumadins. This development has been slow because of technical difficulties, cost of development, cost of trials requiring high sample volumes and long duration of follow up. Therefore usually these drugs are tried in venous thrombosis; if useful in this indication, the results can be extrapolated to other indications. Trials of venous thrombosis can be of shorter duration than the AF – outcome trials, hence are more convenient. Starting from “accidental” discoveries, oral anticoagulants have now come in forefront in the form of scientific proofs by way of large randomized controlled trials. Apixaban for reduction in stroke and other thrombo-embolic events in AF (ARISTOTLE), Dabigatran versus Warfarin in AF (RELY), Rivaroxaban also in AF (ROCKER AF) - used once daily as compared other trials with twice a day dosing.

Historically, newer oral anticoagulants were developed to show “non inferiority” to Warfarin. But Dabigatran, Apixaban & Rivaroxaban have gone even further. They have favourable effect and bleeding profile; once cost and once a day dosing are worked out, these agents, alongwith Edoxaban (ENGAGE AF TIMI 48) are likely to surpass Warfarin.

COAGULATION CASCADE AND SITES OF ACTION OF NEWER ORAL ANTICOAGULANTS (FIG 1):
1. Contact with foreign body (e.g. catheter tip) activates intrinsic pathway. Activation of Xlla, Xla,
IXa, Villa finally activates factor X to Xa. (Monitored by aPTT).

2. Vascular injury activates tissue factor extrinsic pathway. It, through activated Villa finally activates factor X to Xa.

3. Vit K acts through activation of Villa in intrinsic pathway and mainly converts factor II (Prothrombin) to IIa (thrombin) [Monitored by PT (INR)].

4. Xa along with Va converts prothrombin to thrombin (II to IIa).

5. Thrombin in turn stimulates V, VII, VIII, IX and XIII.

6. Thrombin converts factor I (Fibrinogen) to la (fibrin).

7. Fibrin is converted to cross linked fibrin clot by XIII a.

Coumadins act as Vit K antagonists requiring monitoring of PT (INR).

Oral direct Xa inhibitors Rivaroxaban and alike drugs act as inhibitors of activated Xa.

Dabigatran / Ximelgatran act as direct thrombin (IIa) inhibitors. Thus they block conversion of fibrinogen to fibrin and also stimulation of both extrinsic and intrinsic pathways.

Extrinsic pathway activity is monitored by aPTT (activated partial thromboplastin time). Direct inhibition of factor Xla (APIXABAN, etc) cause more coagulation specific effects. Direct thrombin (factor IIa) inhibitors (Dabigatran) have beneficial effects. Outside coagulation cascade also by interfering with effects of thrombin on other sites. Argatroban, Ximelgatran, Dabigatran are univalent oral drugs (Hirudin, Bivalirudin are bivalent IV drugs). Their action prevents fibrin formation and also thrombin mediated activation of factors V, VIII, XI, XIII and thrombin induced platelet aggregation (Fig 1).

DIRECT THROMBIN INHIBITING ORAL ANTICOAGULANTS:

XIMELGATRAN:

First evaluated in orthopedics trials (DVT in peri surgical environment), where it showed superiority over Warfarin.

Efficacy and superiority over Warfarin in stroke prevention in AF was demonstrated in SPORTIFF III and V trials.9

Hepatotoxicity, more than 3 times the upper limit of normal of raised hepatic enzymes was noted in 6.1% cc compared to .8 of Warfarin.

Withdrawn from all markets and from all further developments in February 2006, due to hepatotoxicity. DABIGATRAN (Dabigatran etexilate):

Acts on free thrombin and fibrin bound thrombin also. (Therefore prevents thrombus expansion).

Direct reversible thrombin inhibitor.

Oral prodrug, 6.5% Bioavailability.

80% renal excretion, 12 to 17 hours half life.

Does not require dose monitoring/ PT INR.

Thrombin clotting time/ Ecarin clotting time can be measured in case of bleeding. aPTT may be indicative of Dabigatran effect in case of emergency.

100 to 150 mg twice daily orally.

Dabigatran has shown no hepatotoxicity. It has no interaction with cytochrome P450.

However P-glycoprotein inhibitors such as Amiodarone, Verapamil and Quinidine (all used in patient of AF) may lead to increased plasma levels of Dabigatran, leading to increased bleeding risk. Because 80% of the drug is excreted by kidneys, caution is exercised to adjust doses for age and for renal function.

Dabigatran is considered safe for co-administration with Diclofenac, Atorvastatin, Digoxin, Enoxaparin and maintenance doses (75mg) of Clopidogrel. Adverse events are mainly related to bleeding episodes but no other drug specific adverse event is documented so far.

Dabigatran should be discontinued for 24 hours before invasive procedures and 48 hours before procedures with high risk of bleeding. If renal dysfunction exists with creatinine clearance below 50 ml/min, more than 4 days withdrawal is warranted. aPTT test (though less
precise to judge effect of Dabigatran) can be performed 6 hours before surgery to be sure of safety. If bleeding occurs in a patient while on Dabigatran (e.g. road traffic accident), there is no specific antidote.

Discontinuation of drug controlling source of bleeding, maintain adequate diuresis. Fresh frozen plasma does not reverse effect of Dabigatran. Therefore recombinant activated factor VII (F Vila) or Prothrombin complex concentrates (PCC) are correct theoretical choices. In dire emergencies hemodialysis or charcoal filtration could be attempted. For overdose of Dabigatran, charcoal could be administered within 2 hours of the last dose. VTE prevention trials (Renovate, Remodel, Remobility, Recover) of Dabigatran: Dabigatran was compared to enoxaparin following hip arthroplasty and orthopedic surgeries. Was non inferior at 33 days without increasing bleeding. Meta analysis of these four trials indicates Dabigatran 220 mg once daily orally compared to 40 mg SC of Enoxaparin once daily, is associated with similar efficacy in preventing VTE and all cause mortality. For knee replacement: 110 mg orally 4 hours after surgery and 220 mg once daily for 10 days. For hip replacement: 110 mg orally 4 hours after surgery and 220 mg once daily for 28 to 35 days. % dose to be used for patients above 75 years of age, and in creatinine clearance of 30 to 50 ml/min.

VTE treatment trials (Recover I, II, Remedy) of Dabigatran: Recover I had 2564 patients of acute VTE and compared Dabigatran 150 mg twice daily with Warfarin to maintain INR between 2 and 3. Initial treatment was with parenteral anticoagulation for 8 to 11 days. P value for primary outcome was <0.001 for non inferiority. Major bleeds were similar (less than 2%) and risk of any bleeding was lower in Dabigatran (P < 0.001). Adverse event leading to withdrawal of study drug was 9% (Dabi) to 6.8% of Warfarin (P = 0.05). AF trials of Dabigatran:

AF trials for stroke prevention PETRO & RELY. RELY included 18113 patients with AF fixed dose 110 or 150mg BD of Dabigatran or Warfarin. Follow up of 2 years. High dose prevented more strokes at cost of higher bleeding than Warfarin. (High dose 150 mg twice, low dose 110 mg twice)Low dose caused equal efficiency to Warfarin with lesser bleeding episode. In general found to be safer than Warfarin without losing effect. (Figs. 2 and 3). Intracranial bleeds consistently low in both dosing as compared to Warfarin. For unknown reasons, high dose Dabigatran had higher incidence of myocardial infarction as compared to Warfarin (0.7% Vs 0.5% P = 0.048). In meta analysis of comparing Dabigatran to Aspirin monotherapy and Aspirin - Clopidogrel combination, 150 mg BD of Dabigatran reduces the risk of stroke by 63% compared to Aspirin and 61% as compared to dual treatment. In this dose Dabigatran did not increase risk of extracranial or intracranial hemorrhage. ACS trials of Dabigatran:

REDEEM looked at combination of Dabigatran along with Aspirin & Clopidogrel in ACS. Addition of Dabigatan to Aspirin and Clopidogrel after PCI is safe. It has relevance for those patients of AF who need PCI and also to those who have a LV clot. PROPOSED INDICATIONS FOR USE OF DABIGATRAN:

1. For prevention of deep vein thrombosis upto one month after orthopedic surgeries. (Preferred over Enoxaparin and is cost effective).
2. In patients of AF who require Coumadin / VKA therapy. (Cost may match because PT/INR monitoring is avoided).
3. For prevention of strokes in AF (Effectiveness in preventive strokes is proven better, therefore cost of disabling stroke gets saved). 110 mg BD dose was not approved by US FDA because of not offering efficacy advantage. 150 mg BD was approved. 75 mg BD is approved in patients > 80 years of age and those with high risk of bleeding.
4. Those patients of chronic/intermittent AF undergoing PCI, to add to Aspirin and Clopidogrel.

Indications in Pipeline for Dabigatran:

a. Primary prevention of venous thrombo-embolism.
c. Acute coronary syndrome.
d. Pediatric VTE.
e. Mechanical heart valve replacement. AZD0837:

(A new oral anticoagulant under trial)

Phase II trials in AF shows non-inferiority to Warfarin with less bleeding risk.

ORAL FACTOR XA INHIBITORS:

By inhibiting factor Xa, generation of thrombin (I la) from prothrombin (II) is inhibited. Therefore prothrombin time increases in a dose dependent manner. Parenterally acting Xa inhibitors (Fondaparinux) is indirect Xa inhibitor, (requires antithrombin as a co-factor). Rivaroxaban like orally acting factor Xa inhibitors are direct. They don’t activate platelets or induce platelet factor 4, therefore they have a potential use in treatment heparin induced thrombocytopenia also. RIVAROXABAN:

Bioavailability 80%, plasma half life 10 hours.
66% metabolized in liver, remaining unchanged in urine.

Led to 70% to 18% reduction in DVT and non fatal PE compared to Enoxaparin in orthopedic trials.
### Table 1: Comparison of the Hitherto Conducted or Ongoing Phase III Trials in AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study name</th>
<th>Patients</th>
<th>Primary end- point</th>
<th>Secondary end- point</th>
<th>Follow up</th>
<th>Results (Primary Endpoint)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110mg/150mg Warfarin INR2-3</td>
<td>RE-LY</td>
<td>18,113 patients AF 1 risk factor 50% VKA native</td>
<td>Composite: stroke/systemic embolism</td>
<td>1.Myocardial infarction 2.Pulmonary embolism 3.Hospitalization 4.Total mortality 5.Cardiovascular mortality</td>
<td>Event-driven (n=450), &gt; 12 months</td>
<td>Low-dose dabigatran equally effective, high dose superior to Warfarin</td>
<td>Open-label warfarin</td>
</tr>
<tr>
<td>Apixaban 5 mg b.i.d. Aspirin 81-32 mg od.</td>
<td>AVERROES</td>
<td>5,600 patients AF &gt;1 risk factor Intolerant/ unsuitable for VKA</td>
<td>Composite: stroke / systemic embolism</td>
<td>lattice from first dose of study drug to first occurrence of ischemic stroke, hemorrhagic stroke, systemic embolism, myocardial infarction, or vascular death</td>
<td>Event-driven, 36 months</td>
<td>Apixaban superior to aspirin, no increased risk of bleeding</td>
<td>Prematurely stopped after evidence of superiority of study drug to aspirin</td>
</tr>
</tbody>
</table>

Found to be useful in treatment of acute DVT without PE^{16}

Largest application in ROCETAFA^{17} study (Phase III) in which drug was compared to Warfarin in 14000 non valvular AF patients - In combination with Aspirin and Clopidogrel, in ACS, trials are in progress.

APIXABAN:

Bioavailability 0 to 50% (dose related), Half life 12 hours.

Steady state in 3 days.

Eliminated by plasma, urine and faeces.

Drug drug interactions.

Digitalis: None

Diltiazem: ^ Apixaban cmax by 30%.

Ketoconazole: ‘f- Apixaban cmax by 60 to 100%.
Newer Developments in Oral Anticoagulants

Rifampicin: Reduced Apixaban cmax by 50%.
Aspirin + Clopidogrel: No adverse effects.
Naproxen: T Apixaban cmax by 60%.

Indications:
Periorthopedic surgery
Prevention of stroke in AF (ARISTOTLE, AVERROES).

EDOXABAN:
Direct inhibitor of factor Xa.
> 10000 fold greater selectivity for factor Xa relative to thrombin.
Dose adjustments are required for renal impairment and age and low body weight.
Drugs which inhibit P-GP increase cmax of Edoxaban. Therefore dose adjustment is required with Verapamil, Dronedarone, Quinidine, Ketoconazole.
Rifampicin and Digoxin can be safely co-administered.

Studies have been conducted for peri-orthopedic surgery VTE Prophylaxis, AF for stroke prevention but not in acute coronary syndrome. BETRIXABAN: Only direct Xa inhibitor which is minimally excreted in urine making it suitable in CKD.
Aspirin, Clopidogrel combined with Apixaban/Rivaroxaban showed higher incidence of bleeding which was dose dependent. Risk increase with duration of therapy. Low dose aspirin (< 100mg), Clopidogrel (75mg) and INR of 2 to 2.5 to be aimed at to get therapeutic effect without entailing risk of excessive bleeding.

WHERE DO WE STAND TODAY:
The newer oral anticoagulants have opened a new gate to thrombotic disease management.
The awkwardness of Coumadin derivatives is overcome by these drugs because of betterside effect profile, less monitoring.

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Table 2: Comparison of Pharmacokinetic Properties of New Oral Anticoagulants:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (Hours)</td>
<td>1-3</td>
<td>1-3</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>35</td>
<td>87</td>
<td>90-95</td>
<td>40-59</td>
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<tr>
<td>J(2) (Hours)</td>
<td>12-14</td>
<td>8-15</td>
<td>9-13</td>
<td>8-10</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>80</td>
<td>25</td>
<td>66</td>
<td>35-39</td>
</tr>
<tr>
<td>Food effect</td>
<td>Absorption delayed</td>
<td>?</td>
<td>Delayed</td>
<td>No</td>
</tr>
<tr>
<td>Age</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>7</td>
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<tr>
<td>Body weight</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>7</td>
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<tr>
<td>Gender effect</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>7</td>
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<tr>
<td>Safe in pregnancy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP</td>
<td>No</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

Table 3: Drug Interaction Profiles of Newer Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substrate for P-Gp</th>
<th>Interactions like P-Gp inhibitors (Verapamil, Quinidine, Amiodarone) increases blood levels of Dabigatran</th>
<th>Potent inhibitor of CYP3A4</th>
<th>Substrate for P-Gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CYP3A4</td>
<td>Interactions like Rivaroxaban</td>
<td>CYP3A4 inhibitors, Rifampicin Phenytoin, etc reduce levels of Rivaroxaban</td>
<td>P-Gp inhibitors (like in Dabigatran) increase blood levels of Edoxaban.</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rivaroxaban</td>
<td></td>
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<tr>
<td>Edoxaban</td>
<td></td>
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</table>

Table 2: Total Bleeding in the Rely Trial

Rifampicin: Reduced Apixaban cmax by 50%.
Aspirin + Clopidogrel: No adverse effects.
Naproxen: T Apixaban cmax by 60%.

Table 3: All Cause Mortality in the Rely Trial

Studies have been conducted for peri-orthopedic surgery VTE Prophylaxis, AF for stroke prevention but not in acute coronary syndrome. BETRIXABAN: Only direct Xa inhibitor which is minimally excreted in urine making it suitable in CKD.
and overall smoothness of management. Cost continues to be prohibitory especially in Indian context but like many other molecules, Indian brands, wider applications and subsidiaries will come into play as time goes by.

European society of cardiology have recently indicated CHA2DS2-VASC [Congestive heart failure, hypertension, Age ≥ 75, (doubled) diabetes, stroke doubled, vascular disease, age 65-74 and sex category (female)] system, which allows assessment of who may benefit from the anticipated induction of new generation oral anticoagulant for stroke prevention.22

Other than clotting, thrombin acts as via protease activated receptors (PAR) which becomes upregulated during vascular injury leading to atherosclerosis. Most AF patients have atherosclerosis hence it is proposed that Dabigatran may go beyond anticoagulation in modifying atherosclerosis plaques and affecting the favourable outcomes.23 One envisages broadened horizons for use of the new oral anticoagulants to metallic prosthetic valves, for treatment of acute VTE. Coumadins, the age old friends of clinicians may have to make way for newer, smarter, smoother and equally efficient direct thrombin and Xa inhibitors.

REFERENCES

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