INTRODUCTION
The first coumarin derivative was crystallized in 1940 by Karl Link and co-workers.1 Fourteen years later Coumadin (warfarin®) was approved for the use as an oral anticoagulant (OAC) medication and became the most widely prescribed OAC drug. Later, other vitamin K antagonist (VKA) such as phenprocoumon or acenocoumarol (Acitrom®) that differ mainly in their half-life were developed and introduced for clinical use. Despite the disadvantages like narrow therapeutic index, variable pharmacokinetics due to genetic polymorphisms, variable dose response requiring frequent monitoring, numerous drug and dietary interactions, the oral VKA continued to be the most popular OAC as there were no other options.

The introduction of the newer parenteral anticoagulant like fondaparinux (selective factor Xa inhibitor approved in 2001) was a milestone in anticoagulation because it provided proof of the concept of selective factor Xa inhibition with excellent clinical results.2,3 The direct thrombin inhibitor ximelagatran first approved in 2003 was thought to be a breakthrough in oral anticoagulation, but had to be withdrawn in 2006 due to a high incidence of hepatotoxicity.4 Since then, several newer OACs inhibiting a single activated clotting factor either thrombin (factor IIa) (dabigatran etexilate) or factor X (rivaroxaban, apixaban, edoxaban, betrixaban) have been developed. Three of them have now found place in clinical practice in the West: the direct factor Xa inhibitors rivaroxaban, apixaban, and the direct thrombin inhibitor dabigatran etexilate (Table 1). Further factor Xa inhibitors are in development.5 Of these newer anticoagulants only dabigatran is currently available in India at present with edoxaban and rivaroxaban are expected in the near future.

INDICATIONS FOR ORAL ANTICOAGULATION IN THE PRESENT SCENARIO
The increasing need for OAC therapy for prevention and treatment of cardioembolism and venous embolism balanced against the risk of bleeding makes it imperative for the clinicians to optimize their usage. Table 1 summarizes the indications for OAC therapy in the present scenario.

ORAL ANTICOAGULANT DRUGS COMMONLY USED IN INDIA

Warfarin (Coumadin®)
The classical vitamin K receptor antagonist warfarin is a difficult drug to use, with a narrow therapeutic index, with patients on warfarin walking a tight rope between bleeding and clotting. Sixty years after it was introduced warfarin is still the mainstay of OAC treatment in India and also the Western world. More than 2 million North Americans and probably many more Indians take it and this number continues to grow with the aging population. Warfarin comes in many tablet strengths: 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg. Initiation of warfarin at a dose of 4–5 mg daily is recommended, with smaller doses indicated for the elderly or debilitated patient. Loading doses are not recommended. Warfarin may be begun concurrently with low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) and should be overlapped for 4–5 days to prevent rebound thrombosis from fall in protein C levels. Recommended international normal ratio (INR) range is according to indication. Frequency of INR testing is variable over time, dictated by dose response and clinical information. Initially check INR at least four times per week in the first week of therapy followed by every other day until a therapeutic range is achieved and maintained for two consecutive tests. International normal ratio can then be checked twice weekly for next 2–3 weeks as fluctuations are common. When the INR and warfarin dose remain stable for an additional 2–3 weeks the testing interval can be made every four weekly. International normal ratio tests at no greater than 1 month intervals are recommended for patients who have achieved a stable therapeutic INR.

Acenocoumarol/Nicoumalone (Acitrom®)
Acitrom is similar to warfarin but with longer half-life and lesser interactions. It is available as 1, 2 and 4 mg tablets.

NEWER ORAL ANTICOAGULANTS ON THE ANVIL (TABLE 2)
Dabigatran is now available in India while edoxaban and rivaroxaban are expected shortly.

### Table 1 | Indications for oral anticoagulation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Details</th>
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<tbody>
<tr>
<td>Prophylaxis of cardiac thromboembolism in atrial fibrillation (AF)</td>
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<tr>
<td>Severe left ventricular (LV) dysfunction, mechanical heart valves,</td>
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<tr>
<td>bioprosthetic heart valves (first 3 months), intracardiac thrombi,</td>
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<td>heart valve disease with AF, large left atrial (LA) or history of</td>
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<td>embolism/clot</td>
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<tr>
<td>Treatment of deep vein thrombosis (DVT), pulmonary thromboembolism and</td>
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<tr>
<td>prevention of recurrence</td>
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<tr>
<td>Prophylaxis for prevention of venous thromboembolism (VTE) in high-risk</td>
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<tr>
<td>patients, e.g. postorthopedic surgery</td>
<td></td>
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<tr>
<td>Stroke prevention in nonvalvular atrial fibrillation (NVAF)</td>
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<tr>
<td>Embolic peripheral arterial disease</td>
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#### Oral Anticoagulants: Current Indian Scenario

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### ISSUES IN ORAL ANTICOAGULANT THERAPY PECULIAR TO INDIA

In India, currently vitamin K antagonist (VKA) drugs like warfarin remains the number one agent of choice for oral anticoagulation based on physician comfort due to years of usage and the prohibitive cost of dabigatran. There are certain issues with warfarin peculiar to India. Indians with their different dietary habits compared to their Western brethren are more prone for warfarin-food interactions. For example, inconsistent consumption of green leafy vegetables like cabbage, cauliflower, spinach and other foods rich with vitamin K in the Indian diet would prevent the achievement of target INR on patients with warfarin/Acitrom® and cause lability in INR values. A lot of Indians are in the habit of taking over the counter medications [e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)/tramadol] or alternative herbal products/foods (e.g. garlic, fenugreek) for various disorders from body aches to fever to jaundice. These medications again would increase the OAC action of the VKA and may cause bleeding. Paracetamol is a frequently unrecognized cause of over anticoagulation in India. Use of concomitant antituberculous drugs like isoniazid (INH) or rifampicin can also alter INR values and result in under or over anticoagulation. Indians with low body weight and body mass index (BMI) require lesser doses of VKA to achieve target INR compared to their Western counterparts and are more prone to bleeding. Also during concurrent co-morbid illnesses like fever, diarrhoea, etc. lot of Indian patients omit the VKA and end up in problems of low INR or more commonly take antibiotics like metronidazole or macrolides and come with high INR/bleeding. Amoxicillin and clindamycin do not have significant interaction with warfarin and can be safely prescribed. Rarely the patients on VKA develop conditions like viral hemorrhagic fevers (dengue) and cause lability in INR values. A lot of Indians are in the habit of taking over the counter medications [e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)/tramadol] or alternative herbal products/foods (e.g. garlic, fenugreek) for various disorders from body aches to fever to jaundice. These medications again would increase the OAC action of the VKA and may cause bleeding. Paracetamol is a frequently unrecognized cause of over anticoagulation in India. Use of concomitant antituberculous drugs like isoniazid (INH) or rifampicin can also alter INR values and result in under or over anticoagulation. Indians with low body weight and body mass index (BMI) require lesser doses of VKA to achieve target INR compared to their Western counterparts and are more prone to bleeding. Also during concurrent co-morbid illnesses like fever, diarrhoea, etc. lot of Indian patients omit the VKA and end up in problems of low INR or more commonly take antibiotics like metronidazole or macrolides and come with high INR/bleeding. Amoxicillin and clindamycin do not have significant interaction with warfarin and can be safely prescribed. Rarely the patients on VKA develop conditions like viral hemorrhagic fevers (dengue) complicating the overall scenario. Smoking causes enzyme induction and potentially lowers the INR.

Another issue in India is monitoring of warfarin therapy. Majority of places including suburbs of large cities lack proper laboratories with standardized measurement of prothrombin time (PT)/INR. An Indian study had shown that outpatient anticoagulant control was generally poor with inadequate pretherapeutic assessment,
an unacceptably high proportion of subtherapeutic PT/INR values and high complication rates.\textsuperscript{16} Another Indian study showed that the knowledge base of clinicians in a large teaching institution was unsatisfactory as far as OAC targets were concerned.\textsuperscript{17} There was a tendency to under coagulate in view of the perceived risk of bleeding. One Indian study reported that PT monitoring was irregular in 25\% of patients.\textsuperscript{18} They also found that in patients on mechanical heart valves on VKAs the morbidity increased over years of follow-up and inadequate anticoagulation is associated with increased risk of stroke. In order to achieve better patient compliance and target INR values as per the recommended guidelines for OAC there is a pressing need for better patient education and physician/local practitioner update of the various issues involved.

Recent advancements in pharmacogenetics have established that clinical outcomes in OAC therapy are affected by genetic factors. There are large inter-individual and ethnic variations in drug response to warfarin.\textsuperscript{19} Warfarin is metabolized primarily via oxidation in the liver by CYP2C9, and exerts its anticoagulant effect by inhibiting the protein vitamin K epoxide reductase complex, subunit 1 (VKORC1). Two genetic variants known as CYP2C9`2 AND CYP2C9`3 can lead to a reduced activity of CYP2C9. Three single nucleotide polymorphisms (SNPs), two in the CYP2C9 gene and one in the VKORC1 gene, have been found to play key roles in determining the effect of warfarin therapy on coagulation.\textsuperscript{20} These three SNPs play key roles in determining: (1) the dose of warfarin required to produce a therapeutic INR (typically 2–3); (2) the risk of bleeding or of producing supratherapeutic INR (> 4); and (3) the time required to achieve a stable therapeutic dose. This is especially important in the initial phases of OAC therapy. Since CYP2C9 AND VKORC1 act independently, the total genomic based warfarin variability is presently believed to be at least 50\%. So the US FDA in January 2010 made specific recommendations for dosage range initiation in carriers of the CYP2C9 and VKORC1 variants as determined by genotyping test. As no such testing is available in India we do not have such recommendations to help us in warfarin dosage.

WHAT ARE THE ISSUES WITH WARFARIN DOSING IN THE INDIAN POPULATION?

Warfarin is an extremely effective drug for stroke prevention in atrial fibrillation (AF) patients, reducing stroke by 68\% and mortality by 26\%. But about 60\% of patients never get warfarin, around half of patients who do get it stop taking it especially in the developing world, and of those who still take it only half are in therapeutic range. So, only a small minority are well treated.

The anticoagulation consensus guidelines that relate specially to warfarin do not mention the influence of ethnicity on the typical warfarin maintenance dose. In Asians the starting average dose requirement was found to be 3.4 mg versus 5 mg in Whites in one small study.\textsuperscript{21} The lower dose requirement in Asians was sufficiently recognized to warrant special notation in the US FDA approved labeling for warfarin.\textsuperscript{22} In addition to differences in dose there are unanswered question about whether the risks of warfarin therapy also differ by ethnicity. The large trials that established an INR range of 2–3 to balance the benefits with the risks of warfarin therapy were conducted exclusively in Whites. Data from Chinese and Japanese studies suggest that Asians might require lower INR for protection from thromboembolism and might be at increased risk of bleeding at lower INR.\textsuperscript{23,24} Indian studies on warfarin dosing and risk/benefits are lacking.

WARFARIN IN PREGNANCY: THE INDIAN SCENARIO

Vitamin K antagonists like warfarin should be avoided during pregnancy unless absolutely indicated like, e.g. women with mechanical heart valves. Warfarin is associated with up to 5\% risk of teratogenesis if used between 6 weeks and 12 weeks of gestation. It also increases the risk of miscarriage, fetal and maternal hemorrhage, neurological problems in the baby and stillbirth. It is safe after delivery and during breast-feeding. Warfarin is to be avoided if pregnant or if contemplating pregnancy. The 2008 American College of Chest Physicians (ACCP) guidelines\textsuperscript{25} for antithrombotic therapy recommended one of three approaches for anticoagulation during pregnancy:

1. Aggressive adjusted-dose UFH throughout the pregnancy; heparin is administered subcutaneously every 12 hours in doses adjusted to keep the mid-interval activated partial thromboplastin time (aPTT) at least twice control or to attain an anti-Xa level of 0.35–0.70 U/mL. After a stable dose is achieved, the aPTT should be measured at least weekly.
2. Adjusted-dose subcutaneous LMWH throughout the pregnancy in doses adjusted according to weight to achieve the manufacturer’s recommended anti-Xa level 4 hours after subcutaneous injection.
3. Unfractionated heparin or LMWH therapy (as above) until the 13th week, a change to warfarin until the middle of the third trimester, and then restarting UFH or LMWH until delivery.

Long-term anticoagulation should be resumed postpartum regardless of which regimen is used. Heparin can be restarted 12 hours post-cesarean delivery and 6 hours post-vaginal birth, if no significant bleeding has occurred. Heparin is either continued or replaced with warfarin (stopping the heparin when the INR is therapeutic). All this needs close monitoring, frequent visits to an anticoagulant clinic and is difficult to practice in the rural Indian context where these facilities are lacking. The introduction of newer anticoagulants like dabigatran is unlikely to change this scenario as these newer agents are contraindicated in pregnancy as well.

This textbook recommendation for OAC in pregnancy is difficult to practice in India as it is common for pregnancy to be diagnosed late in the first trimester and for patients to continue warfarin\textsuperscript{26} in view of them not being properly briefed earlier about the teratogenic effects. Women of childbearing age receiving warfarin should be warned about the teratogenic and harmful effects of warfarin especially in early pregnancy. They should be advised to use secure methods of contraception while on warfarin. If pregnancy is suspected, early pregnancy test 5 weeks from last menstrual period must be offered. Conversion to therapeutic once daily LMWH prior to conception is difficult to practice in India.

WHAT IS THE ROLE OF NEWER ANTICOAGULANTS IN THE INDIAN SCENARIO?

Current Indications for Newer Anticoagulants\textsuperscript{27}

- Postoperative thrombotic prophylaxis after major ortho-pedic surgery
- Stroke prophylaxis in nonvalvular atrial fibrillation (NVAF)
- Treatment of DVT and prevention of recurrent thrombo-embolism and treatment of pulmonary embolism (PE) are evolving indications.

Advantages and Disadvantages of Newer Anticoagulants\textsuperscript{28}

Advantages

- Rapid onset of action, so no need for bridging therapy
- Short half-life, so easy control of anticoagulant effect
- Little or no food interaction, so no dietary restrictions like warfarin
- Limited drug interactions unlike warfarin
- Predictability of anticoagulation effect without a need for routine coagulation monitoring.
Section 11

Disadvantages
- Prohibitively high cost resulting in poor compliance
- No monitoring is possible if needed
- No specific antidote
- Serious bleeding in renal impaired patients and elderly more than 80 years. If glomerular filtration rate (GFR) is 15–30 mL/min, warfarin should be preferred.

WILL THE NEWER AGENTS COMPLETELY REPLACE WARFARIN?
The obvious first groups of patients who should be candidates for the new drugs are:
- Patients with unexplained poor control due to unavoidable drug interaction (unless contraindicated)
- New patients naive to oral anticoagulation after briefing them on the various issues involved
- Those with unstable INRs on warfarin.

Should we decide to extend the use of these agents to other patient subsets like valvular AF, mechanical valves and hypercoagulable states?29 The answer seems to be no especially in cases with renal failure or gastrointestinal disease (ulcers, polyps, tumors) who are prone to bleed. Also patients with mechanical heart valve prostheses should remain on VKA because the newer anticoagulants have not been tested for this indication. All newer anticoagulants are contraindicated in pregnancy and lactation. It shall be a while before warfarin is replaced in clinical practice!

CONCLUSION
Cost factors, compliance and dietary patterns need to be kept in mind while prescribing OACs in India. It remains to be seen how the new agents will perform in the long run in real-life situations in the Indian population compared to the good old warfarin with which we all are familiar with for over 50 years. Future research should attempted to find out the best pharmacodynamics monitoring tools for factors Xa and IIa inhibitors, the best therapeutic targets and dosing strategies so that we can use OACs in a safe and efficacious manner for various extended indications.

REFERENCES