Anticoagulant Agents

A broad-spectrum of pharmaceutical agents are available which are very commonly used as adjunctive therapy along with blood products in the treatment of patients with haemostatic disorders.\(^1\)\(^,\)\(^2\) Antithrombotic agents are very commonly prescribed for prevention and treatment of venous thromboembolism (VTE), atrial fibrillation (AF), and acute coronary syndromes (ACSs), and prevention of embolism from mechanical heart valves.\(^3\) Both forms, oral and parenteral are very commonly available; each with various indications and therapeutic targets (Figure 1).

**Oral Anticoagulants**

The oral anticoagulation therapy has been used synonymously with the oral vitamin K antagonists (VKAs) until recently when the advent of the novel agents has broadened the use of this term.

**Vitamin K Antagonists**

The first class of the oral anticoagulants available was the coumarin derivatives and around 1-2% of adults in the modern world have been taking VKA in the form of warfarin or acenocoumarol, etc.\(^5\) Vitamin K antagonists are very commonly used in the prevention of thromboembolism from AF and VTE, management of patients with mechanical heart valves, secondary prevention following stroke and ischaemic heart disease.\(^6\)\(^,\)\(^7\) Their efficacy has been recognised well, but several limitations such as narrow therapeutic index, frequent monitoring, bleeding complications and numerous drug and food interactions make their use quite challenging. Nevertheless, they remain the mainstay of oral anticoagulation therapy.\(^8\)

The main challenges faced in clinical practice while using VKAs are:
1. Narrow therapeutic window
2. Exhibition of considerable variability in dose response among patients due to genetic and other factors\(^*\)\(^9\)

### Figure 1: Currently available antithrombotic agents and their targets

In a recent study by Nahar et al, it was concluded that genetic bleeding risk score (GBRS)\(^*\)\(^{AC+Wf}\) was validated to perform better than the clinical (non-genetic) bleeding risk score (CBRS) as the sensitivity increased 2-folds. Genetic screening for bleeding risk using the current simple scoring method has the potential to remove some of the scientific uncertainties in toxicity cases. It was also concluded that predictive bleeding score helps in improving the quality of anticoagulation by careful INR monitoring, proper management guidelines and patient education regarding concomitant drugs, vitamin K diet and signs of bleeding can decrease the incidence of bleeding complications. This can greatly reduce the economic burden of adverse drug reactions.
3. Subject to interactions with drugs and diet
4. Laboratory control is difficult to standardise
5. Maintenance of a therapeutic level of anticoagulation requires a good understanding of the pharmacokinetics and pharmacodynamics of VKAs and good patient communication.

**Mechanism and Pharmacology**

Vitamin K antagonists act by competitively inhibiting enzymes involved in hepatic synthesis of the vitamin K-dependent coagulation factors II, VII, IX, and X, as well as the natural anticoagulants protein C and protein S.

**Pharmacokinetic Comparison between Warfarin and Acenocoumarol**

Warfarin and acenocoumarol, though having the same acting mechanism (Figure 2), have significant differences in their pharmacokinetic properties. Various pharmacokinetic parameters of both these VKAs have been described in Table 1.10,11

The favourable pharmacokinetic properties of acenocoumarol are as follows10,11:
- Acenocoumarol has a rapid onset of action, and the effect is maintained for 15-20 hours. Such properties offer great advantages to its clinical use.
- In most of the patients, it induces the therapeutic prothrombin level 36 hours after the initial dose.
- Therapeutic international normalised ratio (INR) values are easy to maintain with single daily dose of acenocoumarol and dose titration of acenocoumarol can be done as per the protocol provided in Table 2.12

**Table 1: Comparison of pharmacokinetic properties of warfarin and acenocoumarol**10,11

<table>
<thead>
<tr>
<th>Properties</th>
<th>Warfarin</th>
<th>Acenocoumarol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>99.4%</td>
<td>60%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Very high (99%)</td>
<td>Very high (98.7%)</td>
</tr>
<tr>
<td>Half-life</td>
<td>Distribution: 6–12 hours</td>
<td>Elimination: 20–60 hours (mean 40 hours)</td>
</tr>
<tr>
<td>Effect on PT</td>
<td>Within 24 hours</td>
<td>15–20 hours</td>
</tr>
<tr>
<td>Time to peak plasma concentration</td>
<td>4 hours</td>
<td>1–3 hours</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>72–96 hours</td>
<td>36–48 hours</td>
</tr>
<tr>
<td>Duration of action</td>
<td>2–5 days</td>
<td>48 hours</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal 92%</td>
<td>Renal 60%</td>
</tr>
<tr>
<td>Preparations available</td>
<td>1 mg, 2 mg, 3 mg, and 5 mg</td>
<td>0.5 mg, 1–4 mg tablets</td>
</tr>
</tbody>
</table>

**Fig. 2: Site of action of vitamin K antagonist**

**Table 2: Protocol for dose titration of acenocoumarol**13

<table>
<thead>
<tr>
<th>INR</th>
<th>To current dose of acenocoumarol</th>
<th>INR monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.3</td>
<td>Add 1 mg/day</td>
<td>Repeat INR after 1 week</td>
</tr>
<tr>
<td>1.4–2</td>
<td>Add 0.5 mg/day</td>
<td>Repeat INR after 1 week</td>
</tr>
<tr>
<td>2.1–3</td>
<td>Continue with current dose</td>
<td>Repeat INR after 1 week</td>
</tr>
<tr>
<td>3.1–3.5</td>
<td>Decrease by 0.5 mg/day</td>
<td>Repeat INR after 1 week</td>
</tr>
<tr>
<td>3.6–4</td>
<td>Decrease by 1 mg/day</td>
<td>Repeat INR after 1 week</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>Stop therapy for 3 days</td>
<td>Repeat INR</td>
</tr>
</tbody>
</table>

If INR remains > 4
- Withhold therapy till the desirable INR range is achieved

If INR < 4 on repeated measurement
- Follow as above

INR: international normalised ratio.

**Acenocoumarol offers several benefits over warfarin, such as:**
- More rapid onset of action14
- Shorter half-life14
- Offers better stability of prothrombin time11
- Rapid reversal of anticoagulant action, with relatively smaller dose of vitamin K14
- Less dependence on CYP2C9 enzyme for metabolism14

An observational study conducted to evaluate the
treatment quality with acenocoumarol vs warfarin reported that patients receiving acenocoumarol achieved better INR stability in terms of longer time in therapeutic INR range than those receiving warfarin (37.6% vs 35.7%, p = 0.05). The SPORTIF-III substudy compared acenocoumarol (A) with warfarin (W) in the same group of 74 patients, with chronic AF who started with W and then changed to A for 3 months. It reported that mean percentage of INR in therapeutic range was better with acenocoumarol (56%) than with warfarin (49%, P < 0.05). The incidence of subtherapeutic INRs was higher with warfarin (28%) than with acenocoumarol (19%, P < 0.05). With the advantage of better INR stability at much lesser dose, acenocoumarol was superior in efficacy and safety.

In a study done on 103 patients, who had changed from acenocoumarol to warfarin, to know whether warfarin could improve the quality and the stability of oral anticoagulation and whether there was a difference between the two drugs in the weekly mean dose per patient; it was found that the percentage of prothrombin time (PTs) in the therapeutic range was 59% with acenocoumarol and 62% with warfarin (p = 0.05). The mean number of visits per patient was 12 and 11, and the mean number of visits in the therapeutic range was 7 and 7, respectively. The last check in file method did not show any difference between the two drugs. Overdose states were 51 (4.4%) with acenocoumarol and 30 (2.8%) with warfarin (p = 0.05). A good correlation (r = 0.92) was found between the acenocoumarol and the warfarin weekly mean dose (Figure 3). The mean warfarin/acenocoumarol weekly dose ratio was 2.08 (range: 1.25-3.30; CI 95%: 1.99-2.16). The report concluded that warfarin did not improve the condition of the patients who changed from acenocoumarol to warfarin and the differences between two drugs are not important in the clinical practice.

New Oral Anticoagulants

The novel oral anticoagulants (NOACs) were developed with more pharmacokinetic-pharmacodynamic relationships, faster onset of action, and fewer potential interactions. The two main classes developed were direct thrombin inhibitors and factor Xa inhibitors.

Various pharmacokinetic parameters of three recently available NOACs have been summarised in Table 3.

The major highlights of the NOACs are as follows:

- The NOACs vary widely in their pharmacokinetic properties.
- The bioavailability of rivaroxaban is high, while that of dabigatran is much less.
- The half-life of these agents is variable in normal individuals and patients.
- The elimination of dabigatran depends largely on renal excretion; patients with renal impairment are exposed to higher levels of dabigatran for a longer duration. Dose adjustment is suggested in such cases.
- Although drug interactions with NOACs are not as frequent as with the older ones, drug interactions do occur and affect the pharmacokinetic parameters of these drugs.

Few challenges in the adoption of NOACs into clinical practice have been highlighted in Figure 4. The conventional oral anticoagulants, despite having many drawbacks, remain the mainstay of oral anticoagulation therapy. Although newly introduced novel anticoagulants offer some benefits over the conventional ones, they have their own set of disadvantages. The advantages and disadvantages of the NOACs vs the conventional VKAs are listed in Table 4.

The effects of the novel anticoagulants are usually predictable, with lesser inter- and intra-patient variations. Early studies have demonstrated relatively lesser incidence of major bleeding events with the use of NOACs. They have lesser interactions with foods and other drugs. This eliminates the need of therapeutic monitoring with any modification in the medication profile of the patient. Although arguable, lesser need for frequent monitoring may reduce patients’ inconvenience.

The twice-daily regimen of these NOACs may not be preferred by patients and may lead to poor patient compliance. In patients with poor adherence to therapy, the risk of stroke or systemic embolism is increased. The risk of stroke or systemic embolism will be increased in those patients who do not adhere
Table 3: Pharmacokinetic features of novel oral anticoagulants\textsuperscript{16,17}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>80–100%</td>
<td>50–85%</td>
<td>~6.5%</td>
</tr>
<tr>
<td>Time to peak drug levels</td>
<td>2–4 hours</td>
<td>3 hours</td>
<td>0.5–2 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>5–9 hours in healthy subjects</td>
<td>9–14 hours</td>
<td>11 hours in healthy young subjects</td>
</tr>
<tr>
<td></td>
<td>7–11 hours in patients</td>
<td></td>
<td>14–17 hours in patients</td>
</tr>
<tr>
<td>Elimination</td>
<td>66% renal</td>
<td>27% renal</td>
<td>80% renal</td>
</tr>
<tr>
<td></td>
<td>33% faecal</td>
<td>63% faecal</td>
<td>20% faecal</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP 3A4 inhibitor</td>
<td>CYP 3A4 inhibitor</td>
<td>PPIs decrease absorption</td>
</tr>
<tr>
<td></td>
<td>P-GP inducers/inhibitors</td>
<td>P-GP inducers/inhibitors</td>
<td>P-GP inducers/inhibitors</td>
</tr>
<tr>
<td>Antidote</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>2–4 hrs</td>
<td>3–4 hrs</td>
<td>2 hrs</td>
</tr>
<tr>
<td>Dose regimen</td>
<td>20 mg/d o.d.</td>
<td>2 × 2.5–5 mg/d b.d.</td>
<td>110/150 mg/d b.d.</td>
</tr>
<tr>
<td>Approved clinical indication</td>
<td>Pulmonary embolism and DVT treatment and reduction in risk of recurrence</td>
<td>Stroke and systemic embolism resulting from non-valvular AF</td>
<td>Reduce the risk of stroke and systemic embolism in patients with non-valvular AF</td>
</tr>
<tr>
<td></td>
<td>DVT prophylaxis after knee or hip replacement surgery</td>
<td>Stroke prophylaxis in patients with non-valvular AF</td>
<td>Postoperative VTE prophylaxis for TKA and THR surgery</td>
</tr>
</tbody>
</table>

P-GP: P glycoprotein; PPIs: proton pump inhibitors; DVT: deep vein thrombosis; AF: atrial fibrillation; VTE: venous thromboembolism; TKA: total knee arthroplasty; THR: total hip replacement.

Fig. 4: Challenges with the use of novel anticoagulants

Table 4: Advantages and Disadvantages of Novel Oral Anticoagulants over Older Oral Anticoagulants\textsuperscript{19}

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-dose regimen</td>
<td>Patient compliance</td>
</tr>
<tr>
<td>Good safety profile</td>
<td>- Twice-daily dosage regimen</td>
</tr>
<tr>
<td>Lesser drug interactions</td>
<td>- Short half-life</td>
</tr>
<tr>
<td>No food interactions</td>
<td>No assay method</td>
</tr>
<tr>
<td>No need of routine monitoring</td>
<td>No antidote</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Dosage modification in renal impairment</td>
</tr>
<tr>
<td></td>
<td>Side effects: Gastric intolerance, dyspepsia, myocardial infarction, minor haemorrhages</td>
</tr>
</tbody>
</table>

No validated tests to assess anticoagulants effect

Balance between cost and efficacy

No antidote for most agents

No established therapeutic range

Assessment of compliance is more difficult

Large sample size needed for head-to-head trials

Interpretation of non-inferiority trials

Potential for unknown long-term adverse effects

to therapy.\textsuperscript{20} No coagulation assay is easily available to precisely measure the anticoagulation effect\textsuperscript{20} as the dose cannot be titrated, the cause of failure of therapy (poor adherence vs failure) cannot be assessed, the degree of coagulation inhibition cannot be easily assessed in emergency situations, such as need for urgent surgery or in patients with life-threatening bleeding. No specific antidote is known till day to reverse the anticoagulant effect of these newer agents. This may be problematic in patients with overdose, or those requiring immediate surgical intervention.\textsuperscript{20} The newer anticoagulants are much expensive than the conventional ones.\textsuperscript{20} Most of the newer anticoagulants depend largely on renal excretion for their elimination. Patients with renal impairment may be exposed to higher levels of such agents. Thus, dosage modifications are required. Some of these agents are contraindicated in patients with severe renal impairment.\textsuperscript{11} The incidence of gastrointestinal side effects such as dyspepsia with dabigatran (reported incidence 12\%) may lead to patient incompliance to the therapy. The incidence of myocardial infarction (MI) and haemorrhage is also a concern with the use of dabigatran.\textsuperscript{15} As the degree of anticoagulation cannot be assessed; bridging the anticoagulant therapy may be problematic.\textsuperscript{19}

With the introduction of NOACs, many clinicians may be eager to switch their patients from VKAs to NOACs. Such a decision may be premature, and a careful judgement of risk-to-benefit ratio of these drugs should form the basis for such a decision.\textsuperscript{19} The major advantage of using novel anticoagulants is that they do not require frequent INR monitoring. Routine monitoring is beneficial in detecting occurrence of potentially harmful situations, such as
overcoagulation, and appropriate dosage adjustments can be done to prevent worsening of the situation. Such incidents also alert the clinicians and the recurrence of overcoagulation can be prevented in future. The guidelines recommend 4-weekly INR monitoring in patients who are on VKAs, recently a study reported that time in therapeutic range of INR was more than 70% with 12-week INR monitoring. Further, fewer patients in 12-week INR monitoring group had any dose changes than in the 4-week monitoring group (p < 0.05). The Home INR Study (THINRS) reported that weekly home-based INR monitoring is as safe as clinical monitoring which may help reduce patient inconvenience by reducing the time spent in the anticoagulation monitoring clinics. The patients have to be trained properly and competence has to be ensured in using home-based INR testing.

The pharmacokinetic studies have reported considerable variations in plasma levels of dabigatran. There may be variability in the therapeutic response of various patients and hence the fixed dose of NOAC does not apply well clinically. The patient compliance reduces by 10% due to the twice-daily dosage of NOAC and its shorter half-life. It is difficult to ensure the therapy in the patient as monitoring is not done and there is a high probability of the patient skipping doses. Vitamin K antagonists have comparatively longer half-lives, so missing an occasional dose may not be problematic. Unavailability of assay method to precisely measure the anticoagulant effect of novel anticoagulants further limits the clinical utilisation of the novel anticoagulants, as measuring the anticoagulant effect may be required in acute conditions such as suspected under- or overdosing, comorbidity, potential interactions, renal impairments (rapid degradation due to dehydration or the use of antibiotics), and in patients undergoing surgery or cardioversion. In the absence of an appropriate assay method, altered renal function may lead to unknown consequences as novel agents depend largely on renal excretion for their elimination. Renal function decreases with age and other comorbidities, making the dosage adjustments necessary.

A recent survey reported that the major concern with the questioned 700 physicians was the cost of therapy NOAC, as the patients tend to skip the doses or do not refill their prescriptions intentionally due to financial constraints. The cost of novel anticoagulants is several times higher than VKAs.

Full spectrum of drug/food interactions is not yet known, and an assay method to determine the effect of such interactions is also not available. This adds to the uncertainty with the use of novel agents. There are few reports of dabigatran being contraindicated in patients receiving quinidine and verapamil. Dose reduction of dabigatran is recommended with concomitant use of amiodarone. Further concomitant use of dabigatran and aspirin is not recommended for the fear of an increased risk of bleeding. Rivaroxaban, being largely metabolised by CYP450 enzymes, is contraindicated in patients receiving ketoconazole, itraconazole, and ritonavir. Concomitant administration of rivaroxaban with strong CYP3A4 inducers (such as phenobarbitone, phenytoin, carbamazepine) should be used with caution. An increased risk of bleeding suggests cautious use of non-steroidal anti-inflammatory drugs with rivaroxaban.

Recent 2013 Congress of the International Society on Thrombosis and Haemostasis meeting in Amsterdam highlighted the risk of MI with dabigatran. The meta-analysis included 10 studies and among the 23,839 dabigatran-treated patients, there were 292 MIs. Compared with warfarin, the risk of MI was increased 38%, while the risk of MI was 70% higher among dabigatran-treated patients compared with placebo-treated patients. In another meta-analysis combined data from 7 studies of dabigatran—the RELY and PETRO trials vs warfarin in AF patients; 3 studies of short-term prophylaxis of deep venous thrombosis with enoxaparin as control; 1 study in acute VTE with warfarin as control; and 1 study in ACS vs placebo. Results showed that dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group.

The rise in gastrointestinal bleeding with the novel agents is a cause of concern, particularly in elderly population. In the absence of a specific antidote to reverse their effect, management of life-threatening bleeding episodes is difficult. Also, the peri-operative reversal and bridging of anticoagulation with the novel agents are not yet determined.

Ansell suggested that there are enough unknowns at the present time to caution healthcare providers against the use of NOAC as first-line therapy for patients with AF.

**Antiplatelet Agents**

Antiplatelet agents act by preventing and/or reversing platelet aggregation in arterial thrombosis and are useful in conditions such as MI and ischaemic stroke. Antiplatelet agents can be classified based on their mechanism of action.

1. **Aspirin** blocks the synthesis of thromboxane A2 because of its ability to bind with cyclo-oxygenase-1 irreversibly.
2. **Thienopyridine class of agents** such as clopidogrel and ticlopidine act by irreversibly blocking the adenosine diphosphate (ADP) receptor.
3. **Glycoprotein IIb/IIIa inhibitors** block the final
pathway of platelet activation, which leads to platelet aggregation.

4. An increase in intracellular cyclic adenosine monophosphate (cAMP) levels are caused by phosphodiesterase inhibitors like dipyridamole and cilostazol leading to inhibition of platelet function (Figure 5). \(^{29}\)

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Guideline recommendations for the prevention of thromboembolism in non-valvular AF recommend that when patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75-100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or — less effectively — aspirin 75-325 mg daily (IIa). \(^{1}\)

The indications for OACs compared to antiplatelet agents and NOACs are given in Table 5. \(^{30-32}\)

The comparative analysis of OAC and antiplatelet agents in various clinical conditions is as follows:

**Stroke Prevention in Atrial Fibrillation**

The choice is made based on the assessment of absolute risk of stroke and the potential for bleeding events and taking into account several patient-related factors such as comorbidities and compliance. Oral anticoagulants are generally recommended for those having a CHA\(_2\)DS\(_2\)-VASC score of 2 or higher, and either aspirin or OAC is recommended for those with CHA\(_2\)DS\(_2\)-VASC score of 1 and either no treatment or aspirin is considered reasonable for those with CHA\(_2\)DS\(_2\)-VASC score of 0. Several prevention trials including Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK-1), Stroke Prevention in Atrial Fibrillation (SPAF-II), SPAF-III, AFASAK-2, and secondary prevention trial—European Atrial Fibrillation Trial (EAFT) revealed a greater reduction in the risk of ischaemic stroke with vitamin K antagonists when compared to aspirin, especially in those at higher risk for stroke. \(^{29,33,34}\)

A meta-analysis showed that adjusted dose VKAs and antiplatelet agents reduced stroke by 64% [95% confidence interval (CI) 49-74%] and 22% (95% CI 6-35%), respectively when compared to the control group. The analysis further indicated that adjusted-dose VKAs were more efficacious than antiplatelet therapy in reducing stroke RRR by 39% (95% CI 22-52%) (Figure 6). \(^{35}\)

The SPAF III, a randomised clinical trial compared the efficacy of a combination of low-intensity, fixed-dose VKAs plus aspirin with conventional adjusted-dose VKA, in 1044 patients with AF having at least one thromboembolic risk factor. The study participants were randomised to receive either a combination of

---

\(^{1}\)Class II conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class IIa weight of evidence/opinion is in favour of usefulness/efficacy.
adjusted dose vKA (INR 2.0–3.0). The study results unequivocally demonstrated that adjusted-dose VKA (target INR 2.0–3.0) reduced the risk of stroke in high-risk patients as opposed to the low-intensity, fixed-dose vKA plus aspirin which was inadequate for stroke prevention in patients with non-valvular AF who were at high-risk for thromboembolism (Figure 7). 36

Data from a meta-analysis, which compared the effectiveness of aspirin, warfarin and other anticoagulants as thromboprophylaxis in patients with non-valvular AF (NVAF) showed that adjusted-dose VKA caused a significant decrease in the risk of ischaemic stroke or systemic embolism compared to aspirin [relative risk (RR) 0.59; 95% CI 0.40–0.86], low-dose warfarin, or placebo. Similarly adjusted-dose VKA was found to be better than aspirin + clopidogrel combination in the prevention of ischaemic stroke or systemic embolism in patients with NVAF (Figure 8). 37,38

In a recent meta-analysis, the incidence of bleeding events was assessed from 5 studies, which compared OACs and aspirin. The analysis of these randomised trials indicated no significant increase in major bleeding events in adjusted-dose anticoagulation-treated patients. A higher rate of intracranial haemorrhage was observed in the SPAF-II study, which was due to 7 intracranial haemorrhages among patients > 75 years old, contributing to an annualised rate of 1.8% compared to 0.8% in patients receiving aspirin. 39

The atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE W) study compared the vascular and bleeding outcomes with VKAs vs clopidogrel-aspirin combination. The trial included 6706 patients with AF having one or more risk factors for stroke who...
were randomly assigned to a VKA (INR target 2.0–3.0) or aspirin (75-100 mg/day) and clopidogrel 75 mg daily. The study was discontinued prematurely because of the substantial evidence of superiority of OAC therapy. About 165 primary events occurred in patients who were on OAC therapy compared to 234 in the clopidogrel plus aspirin group. The results of the study showed VKA to be superior to clopidogrel-aspirin combination in the prevention of vascular events along with a lower risk of major bleeding events.  

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