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Review Article

Use of acenocoumarol in cardioembolic stroke: an evidence-based review

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ABSTRACT

Stroke is the leading cause of long-term disability and the second most common cause of death worldwide. Nearly two-thirds of all strokes represent cerebral ischemia, of which about 15%-30% are of cardioembolic origin. Atrial fibrillation accounts for about 60% of all cardioembolic strokes. Current clinical evidence suggests that oral anticoagulant therapy can prevent around 70% of strokes in patients with atrial fibrillation. Oral anticoagulation therapy is preferred over antiplatelet therapy in patients with cardioembolic stroke. Vitamin K antagonists (VKAs) and nonvitamin K antagonist oral anticoagulants (NOACs) are routinely prescribed oral anticoagulants in patients at risk of stroke; however, there are specific indications where VKA use surpasses NOAC use or there are conditions where NOACs are contraindicated. A group of experts revisited the role of oral anticoagulants in the management of cardioembolic stroke in India with emphasis on VKA, specifically acenocoumarol. This article discusses various aspects of anticoagulation therapy, including the timing of initiation and patient monitoring, in patients with cardioembolic stroke with reference to current clinical evidence and expert opinion based on Indian clinical experience.

Keywords: Acenocoumarol, Atrial fibrillation, International normalized ratio, NOACs, VKAs, Warfarin

INTRODUCTION

Stroke is the leading cause of long-term disability, affecting 26 million people worldwide each year.[1,2] It is the second most common cause of death worldwide. Two-thirds of all strokes represent cerebral ischemia, while the remaining strokes represent intracerebral or subarachnoid hemorrhage. Ischemic stroke has multiple etiologies, including atherosclerosis of the cerebral circulation, occlusion of cerebral small vessels, and cardiac embolism. About 15%-30% of all ischemic strokes are of cardioembolic origin; however, the true burden is likely underestimated.[1] Cardioembolic strokes are frequently more severe and prone to early and long-term recurrences than atherothrombotic strokes. In some reports, as high as two-thirds of ischemic strokes were reported as cardioembolic. Cardioembolic stroke is also associated with higher mortality rates and unfavorable functional outcomes.[3]

Interestingly, although there has been an overall decrease in stroke incidence in the past few decades, cardioembolic strokes have tripled, and this incidence is expected to triple again by 2050 based on projections from high-income countries. Low- and middle-income countries are also likely to show similar trends due to demographic changes, increasing life expectancy, and risk factors for cardioembolism becoming more common. The increase in and aging of the world population and decrease in death rates globally in recent decades could also explain this trend of the epidemiology of cardioembolic stroke.[1-3]

The common causes of cardioembolism include atrial fibrillation (AF), ischemic cardiomyopathy, rheumatic mitral valve disease, left ventricular failure, systolic heart failure, and use of prosthetic valves. AF is the most common etiology for cardioembolic strokes, accounting for about 60% of all cardioembolic strokes.[1] AF is associated with a 3- to 5-fold increased risk of stroke. History of nonvalvular AF is reported in around half of the cases of cardioembolic stroke. History of left ventricular thrombus is reported in almost one-third and that of valvular heart disease in one-fourth of patients with cardioembolic stroke. Rheumatic mitral stenosis is the most common rheumatic valvular disease accounting for cardioembolic strokes.[1,2,4]

Major sources of embolism have an established causal relationship with stroke and are crucial in identifying patients with cardioembolic strokes. It is clinically pertinent as these patients have high recurrence rates and represent a subgroup of patients who may benefit from oral anticoagulation.[1,5]

A group of experts across different regions of India revisited the role of VKAs in the management of cardioembolic stroke with an emphasis on acenocoumarol. Objectives of the review were to collate insights on clinical practice about the management of patients with cardioembolic stroke with different risk factors, to understand the positioning of VKAs and different patient profiles in which they are prescribed, and how patients are managed on a long-term basis.

ROLE OF ORAL ANTICOAGULANTS IN CARDIOEMBOLIC STROKE

Oral anticoagulant therapy can prevent ~70% of strokes in patients with AF.[6] The main indications for oral anticoagulation are AF and status post-heart valve replacement.[7] Long-term oral anticoagulation is prescribed in most patients with AF to decrease the risk of ischemic stroke and other embolic events. The benefit of anticoagulation outweighs the associated increase in the risk of bleeding in these patients. Patients with a diagnosis of first-time AF should usually receive anticoagulation based on the CHA_2DS_2-VASc score where C, H, A, D, S and VASc stand for congestive heart failure, hypertension, age, diabetes, stroke and vascular disease, respectively.[8] In patients with mechanical heart valves, life-long oral anticoagulation with VKAs is recommended. Currently, NOACs are contraindicated in this group of patients.[7,9]

Experts are of the opinion that oral anticoagulation is more effective than antiplatelet therapy in patients with cardioembolic stroke.

Timing for starting anticoagulants post cardioembolic stroke

Cardioembolic stroke has a relatively high recurrence rate in the first 90 days.[10] The timing of starting or resuming anticoagulation to prevent stroke recurrence after a cardioembolic stroke is uncertain. American heart association/American stroke association (AHA/ASA) 2018 guidelines recommend initiating anticoagulation within 4-14 days from the index event after cardioembolic stroke. AHA/ASA guidelines suggest later treatment initiation for patients with hemorrhagic transformation.[11] However, in a multicenter, retrospective real-world cohort study, the recommended 4-14 days to start oral anticoagulation was not associated with reduced ischemic and hemorrhagic outcomes, suggesting reconsideration of the recommendation.[12]

European society of cardiology (ESC) 2016[13] and European heart rhythm association (EHRA) 2018 guidelines endorse early initiation of NOAC after ischemic stroke with AF according to the "1-3-6-12-day" rule.[14] The EHRA-ESC guidelines recommend the administration of anticoagulants one day after the onset of the transient ischemic attack, after three days in patients with a minor stroke, which is defined as national institutes of health stroke scale [NIHSS] score <8, after six days in those with mild stroke defined as NIHSS scores 8-15, and after 12 days in those with severe stroke defined as NIHSS score >15.[13,14] These recommendations are for NOAC, and the question for initiation of VKA post-cardioembolic stroke remains unanswered.

According to the experts, the 1-3-6-12 day rule is appropriate for the NOACs. For VKAs, a little delay is acceptable. Experts further added that the time of initiation of oral anticoagulation post-cardioembolic stroke depends on the size of the stroke, whether it was a transient ischemic attack (TIA), minor stroke, or a moderate cortical stroke. In the case of TIA, anticoagulation may be initiated just 24 hours after the event. If it is a minor stroke, anticoagulation is generally initiated between 3 and 7 days, depending on the etiology in the cardioembolic subgroup. The presence of a left ventricular thrombus or a mechanical valve thrombus indicates an earlier initiation of anticoagulation, considering the risk of hemorrhagic stroke conversion. Anticoagulation is typically initiated at least two weeks after the event if the stroke is moderate to large cortical infarct, which may have a very high risk of hemorrhagic conversion. In the case of lone AF, a delay longer than two weeks is concerning if the stroke is large and if a patient has a thrombus or mechanical valve thrombus.

Choosing VKA over NOAC: clinical scenarios and indications

There are certain indications for oral anticoagulation therapy where VKAs continue to be the standard of care. VKAs should be used preferably in patients with valvular heart disease. Patients with a mechanical heart valve of any type and location, patients with severe or clinically significant rheumatic mitral stenosis having mitral valve area ≤1.5 cm, and patients implanted with a bioprosthetic valve should receive VKA anticoagulation therapy.[7,14,15]

Apart from apixaban, other NOACs are not recommended for patients with creatinine clearance <15-30 mL/min or those on dialysis.[16] NOACs are also contraindicated in patients with child-Pugh category C hepatic insufficiency. In these clinical scenarios, VKAs can be prescribed preferably. It is suggested that NOACs should also not be used in individuals younger than 18 years of age and elderly patients where VKAs can be preferred.[7,14,15]

It is reasonable to prefer VKAs over NOACs in patients not likely to comply with the twice-daily dosing of dabigatran and apixaban or unable to take once-a-day rivaroxaban due to toxicity. Patients on NOAC therapy for AF can be switched to VKA if the patient develops severe kidney disease or if there is a contraindication to NOAC use. The switch is also preferred when the treatment cost is unacceptably high for patients.[7,14,15]

Experts agreed that VKA is preferred over NOAC in patients with a mechanical heart valve, and it should also be used preferably in patients with valvular heart disease.

Monitoring of patients on oral anticoagulation with VKA

Monitoring oral anticoagulation therapy is imperative in maintaining the appropriate levels of anticoagulation and balancing the risk of thrombosis and bleeding. International normalized ratio (INR) is the test of choice for monitoring patients on VKA treatment. INR can also be used to assess the risk of bleeding or the coagulation status of patients.[17,18,19,20]

For patients with AF treated with VKA, an INR target of 2-3 is recommended, with an average annual time in the therapeutic range (TTR) of more than 70%. This recommendation is based on findings that the risk of stroke significantly increases with INR values <2 and the risk of bleeding increases with INR >3.[18,21] Recommended INR between 2 and 3 is irrespective of age (Table 1).[18,19,20,21]

Experts also agreed that INR values should be generally maintained at 2-3, preferably at 2.5. However, in patients with a prosthetic valve, a value between 2 and 3.5 should be preferred to reduce the risk of stroke. Experts also mentioned that there is a need for standardization of INR estimation as variations may affect treatment decisions and clinical outcomes.

Deciding on the appropriate VKA: Warfarin or acenocoumarol?

Acenocoumarol presents some pharmacokinetic and pharmacodynamic differences from warfarin that may be useful in some patients (Table 2). Acenocoumarol also has a more rapid onset of action, a shorter half-life, superior anticoagulant stability, rapid reversal of anticoagulation effect, less dependence on CYP2C9 enzyme for metabolism, and lower renal excretion compared with warfarin.[19,22,23,24,25] The half-life of acenocoumarol is similar to that of NOAC.

Patients with a higher number of comorbidities and on antiplatelet agents are more frequently prescribed acenocoumarol instead of warfarin. The shorter half-life of acenocoumarol adds an advantage in the case of major or life-threatening bleeding where a rapid offset of action of the drug is required.[26] The reversal of the anticoagulant effect of acenocoumarol can be achieved within a few hours with a relatively lower dose of vitamin K1.[19]

Less dependence on CYP2C9 enzyme for metabolism is an added advantage of acenocoumarol over warfarin.[22] The CYP2C9 genotypes influence the pharmacokinetics and pharmacodynamics of VKAs. The CYP2C9 polymorphism delays the stabilization of coumarin anticoagulants. The effects of CYP2C9 polymorphisms on the pharmacokinetics and anticoagulant response are less pronounced with acenocoumarol than warfarin.[27]

Earlier it was assumed that the shorter half-life of acenocoumarol is also associated with the risk of factor VII fluctuations. However, the assumption was proven wrong by a comparative study conducted by Barcellona and colleagues.[28] The study showed that warfarin was not better than acenocoumarol in terms of prothrombin time (PT) within the therapeutic range per patient. The study also showed that daily fluctuation in factor VII levels was due to the intake of vitamin K and was independent of the drug's half-life. The shorter half-life of acenocoumarol had no impact on it.[28]

The SPORTIF-III substudy showed that acenocoumarol is superior to warfarin in maintaining INR stability within the therapeutic range.[23] In another observational, comparative study conducted by Kulo and coworkers, acenocoumarol showed significantly better anticoagulation stability with therapeutic INR values covering the significantly longer time of treatment. The percentage time of INR values in the therapeutic range was significantly higher with acenocoumarol treatment (37.6%) compared to that with warfarin (35.7%, p=0.0002).[24]

Another prospective observational study published by Alias and coworkers has demonstrated better efficacy and safety of acenocoumarol over warfarin in patients with AF.[29] Efficacy analysis showed that the mean (standard deviation) time in the therapeutic range (TTR) was significantly higher for the acenocoumarol group (56.54% [19.67]) than the warfarin group (50.69% [23.57]; p=0.048). A significantly lower proportion of patients in the acenocoumarol group experienced stroke episodes ((11.01%) compared with the warfarin group (22.01%, p<0.05). Safety assessment showed that more adverse drug reactions were reported in the warfarin group than in the acenocoumarol group. Acenocoumarol was also better than warfarin in improving the quality of life of patients.[29]

Experts also agreed that acenocoumarol has an advantage over warfarin and should be the choice of oral anticoagulant in these patients.

Table 1: Recommended target INR for VKA therapy.

Indication	Recommended INR
AF	2.0-3.0
Post-myocardial infarction (with increased risk for thromboembolic complications)	2.0-3.0
Rheumatic mitral valve disease	2.0-3.0
Bio-prosthetic heart valves	2.0-3.0
Mechanical heart valves	2.0-3.5

Table 2: Comparison of pharmacokinetic properties of warfarin and acenocoumarol.

Properties	Warfarin	Acenocoumarol	Clinical implication
Absorption	Rapid	Rapid	Rapid absorption implies rapid onset of action
Bioavailability	99.4%	60%	-
Protein binding	Very high (99%)	Very high (98.7%)	-
Half-life	Long (30-80 hours)	Short (8-11) hours	Shorter half-life implies rapid onset of action and rapid reversal of anticoagulant effect with lower dose of vitamin K1
Effect on prothrombin time	Within 24 hours	15-20 hours	Shorter prothrombin time implies rapid reversal of anticoagulant effect and lower risk of prolonged bleeding
Time to peak plasma concentration	4 hours	2-3 hours	Shorter time implies rapid onset of action
Time to peak effect	72-96 hours	36-48 hours	Shorter time implies rapid onset of action
Duration of action	2-5 days	48 hours	Shorter duration of action implies ease of dose titration and control of the duration of anticoagulation and lower risk of prolonged bleeding
Elimination	Renal 92%	Renal 60% Fecal 29%	Lower renal excretion implies reduced risk of accumulation and potential toxicity in patients with impaired renal function

ACENOCOUMAROL FOR PRIMARY AND SECONDARY PREVENTION OF CARDIOEMBOLIC STROKE

Efficacy of acenocoumarol

Efficacy and safety of acenocoumarol have been studied in a wide range of indications requiring prevention and treatment of thromboembolism, including AF, cardiac valve replacement, and after myocardial infarction, which are the most common risk factors and etiologies of cardioembolic stroke.

As shown in a study by Barcellona and colleagues, the values of prothrombin time remain in the therapeutic range with acenocoumarol in patients treated for a wide range of indications. The patients in this study received acenocoumarol for the indications including mechanical heart valves, biological heart valves, rheumatic AF, recurrent deep vein thrombosis, embolic stroke, previous myocardial infarction, and mitral stenosis.[28]

As discussed earlier in review, the percentage time of INR values in therapeutic range remains high with acenocoumarol treatment. Acenocoumarol has also demonstrated significantly better anticoagulation stability with therapeutic INR values covering significantly longer time of treatment compared to patients with chronic AF and nonvalvular AF.[23,24] Acenocoumarol has also shown a reduction in incidence of stroke in patients with AF.[29]

A Spanish study has documented 10-year experience with acenocoumarol treatment. The most common indication for using acenocoumarol was AF, where around 73% of the patients received acenocoumarol. In 82.5% of the patients treated with acenocoumarol, the INR values were in the therapeutic range of 2.0 to 3.0.[30]

The study compared either acenocoumarol or aspirin in patients with AF. The study showed that acenocoumarol lowers D-dimer content, prevents its formation, and promotes lysis of left auricular thrombi. It also further reduces the risk of the development of ischemic stroke in patients with AF and an elevated risk of thromboembolism. According to the study, acenocoumarol therapy should be preferred over aspirin in patients with AF.[31]

An observational, randomized, prospective–retrospective study evaluated warfarin and acenocoumarol in patients with nonvalvular AF. The study showed that the values of INR were within the therapeutic range of 2-3 in both groups.[32] A population-based retrospective cohort study compared outcomes with acenocoumarol and NOAC

treatment in people with nonvalvular AF in real-world clinical practice.[33] The study found no differences in mortality risk, ischemic stroke, or gastrointestinal bleeding with acenocoumarol or NOAC. Subgroup analysis showed that apixaban was associated with a higher risk of ischemic stroke in high-risk persons (≥75 years and CHA_2DS_2-VASc score ≥2).[33]

Cardiac valve replacement is another indication for acenocoumarol therapy, where long-term anticoagulation is required. A study by Altman and colleagues demonstrated that acenocoumarol in combination with aspirin and dipyridamole in patients with mechanical substitute heart valves effectively maintains the INR levels within the therapeutic range of 2-3 and provides good protection from thromboembolism.[34]

A prospective, randomized study evaluated the effect of acenocoumarol on left ventricular thrombosis in patients with recent myocardial infarction. In this study, acenocoumarol significantly resolved the thrombus at one year of treatment in 88.2% of patients ($p<0.001$). The resolution of thrombus was reported in nearly half of the patients (52.9%) on the 15th day of the treatment. The study concluded that acenocoumarol therapy started early, within five weeks after acute myocardial infarction effectively resolves left ventricular thrombus.[35]

Dosing of acenocoumarol

Acenocoumarol dosing must be individualized. Acenocoumarol is to be administered as a single oral dose and should always be taken at the same time of day. It is suggested that acenocoumarol should not be used when monitoring is impossible.[19,20] The initial recommended dose is 2 to 4 mg/day. Treatment may also be initiated with a loading dose regimen on the first day, usually at a 6 mg dose, and may be followed by a 4 mg dose on second day. Caution should be instituted when the thromboplastin time is abnormal before treatment initiation.[19,20] Maintenance dose of acenocoumarol must be individualized based on PT/INR values. Maintenance dose generally lies between 1 and 8 mg daily.[19,20] Optimal intensity of anticoagulation is aimed at INR values of 2.0 and 3.5, depending on indication (Table 1). Post-myocardial infarction patients may need INR between 3.0 and 4.0.[19]

Experts advised that the timing to take a VKA should be adjusted in relation to food. It should preferably be given around 5 pm so that it does not interfere with lunch/dinner.

Withdrawal of acenocoumarol is generally not associated with the danger of reactive hypercoagulability; hence it is not necessary to give gradual diminishing doses. However, in some high-risk patients like post-myocardial infarction patients, gradual lowering of dose is required.[19,20]

Acenocoumarol is not recommended for patients with severe renal or hepatic impairment due to the increased risk of hemorrhage. Care should be taken in patients with mild to moderate renal or hepatic impairment.[19,20] As there is limited experience with oral anticoagulants, including acenocoumarol, in children, more frequent monitoring of PT/INR is recommended.[20] Wood et al documented long-term experience of acenocoumarol plus aspirin in children aged 5 months to 16 years with cardiac valve replacement. They found no major difficulties in managing anticoagulant treatment and its association with antiplatelet drugs in these children.[36] Bonduel and colleagues reported that implementation of an age-adjusted loading dose regimen allows most children in all age groups to achieve TTR in less than one week.[37] Elderly patients, patients with liver disease or severe heart failure with hepatic congestion, or malnourished patients may require lower doses during the treatment initiation and maintenance phases. Further, more frequent monitoring of PT/INR is recommended in these patients.[19,20] Acenocoumarol is contraindicated in pregnancy, in patients hypersensitive to acenocoumarol, excipients or coumarin derivatives, and for conditions where the risk of hemorrhage is more than the potential benefit.[19,20]

Interruption of oral anticoagulation is required in 10%-20% of all patients undergoing surgery or interventional procedures every year.[7] Bridging anticoagulation in patients with AF who need interruption of VKA for procedures is a clinical dilemma. Guidelines recommend considering the stroke and bleeding risk; however, no clear thresholds are advised. The patient's post-procedural INR management should also be considered while making the decision to bridge anticoagulation. A study showed that in real-world practice, only a small subset of patients benefited from bridging VKA anticoagulation treatment.[38]

Switching between warfarin and acenocoumarol

In the SPORTIF-III substudy, patients with AF who were started on warfarin were switched to acenocoumarol. The warfarin/acenocoumarol dose ratio was 2.18±0.78. There was a good correlation between doses of acenocoumarol and warfarin ($r=0.65$, $p<0.001$).[23] In another study by Leeuwen et al, a transition algorithm was developed for the maintenance dosages of coumarins. The transition factor for acenocoumarol to warfarin was 1.85 (95% confidence interval CI=1.78-1.92), while the transition factor for warfarin to acenocoumarol was 0.53 (95% CI=0.51-0.55).[39] It is important to note that acenocoumarol provides superior anticoagulation stability at half the dose compared to warfarin (Table 3).

Table 3: Dose conversion chart for warfarin and acenocoumarol.

Warfarin dose (mg)	Acenocoumarol dose (mg)*
2	1
4	2
5	2.5
6	3

*Transition factor of 0.53 is approximated to 0.5 for the calculation.

Experts agreed that these transition factors allow easy calculation of the maintenance dose when it is necessary for a patient to switch from warfarin to acenocoumarol. Switching from warfarin to acenocoumarol is commonly considered in patients requiring a very high dose of warfarin, patients not achieving target INR, or in patients developing warfarin resistance.

Based on the genotyping, a polymorphisms-specific algorithm has also been proposed for more accurate acenocoumarol dosage prediction. However, current prescription information does not provide directions for dosing based on pharmacogenetic information. Patients with high or low dose requirements are likely to benefit the most from genetic testing prior to VKA initiation. It is reported that CYP2C9 and VKORC1 variants influence the risk of over-anticoagulation during initiation of the VKA treatment; however, they have limited impact on TTR during the maintenance phase of treatment.[18]

Safety of acenocoumarol

A narrow therapeutic index and unpredictable dose-response pattern are the challenges for the use of VKAs, which can cause side effects. The most common side-effect associated with acenocoumarol is hemorrhage in various organs. Possible sites of hemorrhage include the gastrointestinal tract, brain, urogenital tract, uterus, liver, gall bladder, and the eye.[19]

The occurrence of acenocoumarol-associated hemorrhage is related to dosage, patient age, and nature of the underlying disease; however, it is not associated with the duration of treatment. A prospective observational study by Freixa and colleagues found that the risk of bleeding is significantly high in patients with an INR >5. Oral anticoagulant therapy should be considered carefully in patients with an artificial heart valve, those suspected to have poor treatment compliance, in patients with need for addition of potentially interactive new drugs, and those with a history of an intercurrent disease in the last month.[40]

An Italian prospective cohort study showed that acenocoumarol anticoagulation is well tolerated and safer with proper monitoring. The study highlighted that anticoagulation intensity should be closely monitored to reduce periods of overdosing and, ultimately, to reduce the risk of associated side effects.[41] The Spanish study discussed earlier showed that age is not associated with a higher risk of bleeding, and acenocoumarol can be safely used in the elderly.[30]

Drug interactions have also been found to be a cause of over-anticoagulation with acenocoumarol. Several antibacterial drugs are reported to strongly increase the risk of over-anticoagulation with acenocoumarol. There are differences in the induction period of over-anticoagulation with different antibacterial drugs. These drug interactions should be considered while prescribing antibacterial drugs in patients treated with acenocoumarol.[42] The use of sulfamethoxazole-trimethoprim and amoxicillin plus clavulanic acid should be reconsidered and avoided in patients receiving acenocoumarol. In case of absence of therapeutic alternatives, increased monitoring of INR values is warranted to prevent over-anticoagulation and associated potential bleeding complications.[43]

Clinically insignificant hemorrhages, such as a brief nosebleed or small isolated hematomas, can be managed with a temporary reduction or omission of the dose of acenocoumarol. While in cases of moderate to severe hemorrhage, vitamin K1 (phytomenadione) can be given orally as an antidote. However, high doses of vitamin K1, usually more than 5 mg, can cause resistance to further anticoagulant therapy for several days.[19]

Replenishment with factor concentrate has been shown to be beneficial in reversing VKA anticoagulant activity.[44,45] Hence, in case of life-threatening hemorrhage, intravenous transfusions of fresh frozen plasma or whole blood, complex concentrate, or recombinant factor VII must be supplemented with vitamin K1 to replenish the factor concentrate for rapid reversal of the anticoagulation effect of acenocoumarol.[19]

Key recommendations from the expert discussion are summarized in Table 4.

Table 4: Summary of expert opinions on use of VKAs.

S. no.	Expert recommendations
1	Time to start oral anticoagulation after cardioembolic stroke depends on stroke size and type (TIA, minor, or moderate cortical stroke).
2	Patients with TIA can be anticoagulated 24 hours after the event.
3	Minor stroke patients generally initiate anticoagulation between 3 and 7 days, based on cardioembolic subgroup etiology. Initiation of VKA post-cardioembolic stroke remains uncertain as guideline recommendations are focused on NOACs
4	Left ventricular thrombus or mechanical valve thrombus presence suggests earlier anticoagulation due to hemorrhagic stroke risk
5	Anticoagulation usually begins at least two weeks post-event for moderate to large cortical infarcts with high hemorrhagic conversion risk

Continued.

S. no.	Expert recommendations
6	VKA anticoagulation is advised for mechanical heart valve patients, severe mitral stenosis, and bioprosthetic valve recipients
7	NOACs are not recommended for low creatinine clearance or dialysis patients, and they are contraindicated in patients with severe hepatic insufficiency
8	VKAs can be preferred in non-compliant patients with NOAC dosing or cost concerns
9	Switch from NOACs to VKAs is reasonable in case of development of severe kidney disease or NOAC contraindication
10	Acenocoumarol, as a VKA, offers faster onset, shorter half-life, stable anticoagulation, rapid reversal, lower reliance on CYP2C9, and less renal excretion than warfarin

CYP2C9, cytochrome P450 family 2 subfamily C member 9; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack; VKA, vitamin K antagonist.

CONCLUSION

Oral anticoagulation remains the choice of therapy in the management of cardioembolic stroke. It has to be noted that VKAs are preferred over NOACs in patients with a mechanical heart valve and should also be preferred in patients with valvular heart disease. The 1-3-6-12 day rule is appropriate for the initiation of NOACs therapy; however, no uniform rule can be applicable for the timing for initiation of VKAs, which may vary according to patient clinical characteristics. INR values should be maintained at 2-3 to maintain the appropriate levels of anticoagulation and balance the risk of thrombosis and bleeding with VKAs. While higher INR values of between 3 and 3.5 should be considered in patients with a prosthetic valve. Current evidence points towards acenocoumarol as the VKA of choice over warfarin in primary and secondary prevention of cardioembolic stroke. Less dependence of acenocoumarol on the CYP2C9 enzyme for metabolism provides better anticoagulant stability. Acenocoumarol provides better anticoagulation stability at half the dose compared with warfarin. Patients on warfarin can be easily switched to acenocoumarol if patients require a very high dose of warfarin, do not achieve target INR, or have developed warfarin resistance. Acenocoumarol anticoagulation has a favorable safety profile with adequate monitoring. Hemorrhages can be managed effectively, as a rapid reversal of the anticoagulation effect is possible with acenocoumarol. It can be concluded that acenocoumarol is a promising oral anticoagulation therapy in patients with cardioembolic stroke.

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