Update on secondary prevention of ischaemic stroke
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Abstract
Stroke is becoming a major cause of morbidity and mortality in the developing world while the trend is actually downward in the developed nations. This is mostly because of the better recognition, treatment options and secondary prevention in addition to changes in lifestyles. There have been significant developments in the secondary prevention of ischaemic stroke in the last decade alone. Newer medications like direct thrombin inhibitors and factor Xa inhibitors have come into common practice. These medications are either equally effective or even better than age-old warfarin. Unlike previous belief, we now know that mechanical closure of the patent foramen ovale does not reduce the rate of stroke recurrence. There is a hint that dual anti-platelet therapy may reduce early recurrence of stroke. Even more exciting news is that closure of left atrial appendage might totally eliminate the need for oral anticoagulation in selected patient population.

Keywords: Stroke, Secondary prevention, Atrial Fibrillation, Patent foramen ovale.

Introduction
Non-communicable diseases like stroke are becoming the leading cause of death in the developing world. The South Asians who migrate to the western world also have higher risk of stroke. An epidemiological study done in Leicestershire, UK, showed similar incidence of stroke in South Asian and European white populations. Haemorrhagic stroke makes higher proportion (up to 30%) of all kinds of strokes in Asian countries compared to approximately 15% in the developed countries. Unfortunately, measures of secondary prevention of ischaemic strokes are not utilised as much as they are available elsewhere. Here, we will discuss the established and likely-to-be-approved treatment for secondary prevention of ischaemic stroke. The aim of this review is to particularly emphasise on the topics of recent interests.

Classification of Ischaemic Stroke
The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischaemic stroke is the most widely used tool to categorise stroke according to the most likely aetiology. It denotes five subtypes of ischaemic stroke: 1) large-artery atherosclerosis, 2) cardio-embolism, 3) small-vessel occlusion, 4) stroke of other determined aetiology, and 5) stroke of undetermined aetiology. We will discuss the preventative strategies for strokes presumed to be due to cardio-embolism, and then mostly focus on antiplatelet therapy in patent foramen ovale and strokes due to atherosclerosis. The stroke from specific cause depends on the particular aetiology but these also tend to follow general rules like others.

Stroke due to Cardio-embolism
Cardiac sources of embolism have been grouped according to the therapy recommended (Table-1).

Not all high-risk sources demand anticoagulation for secondary stroke prevention. While discussion of the indication in each of these sources is beyond the scope of this review, we will briefly talk about the recent updates available in those areas. Newer anticoagulants other than warfarin have been approved for secondary prevention of stroke only in cases of non-valvular Atrial Fibrillation (NVAF).

CHADS2 (Congestive heart failure, Hypertension, age >75, diabetes mellitus and stroke or Transient Ischaemic Attack [TIA] doubled) score is the most commonly used risk stratification tool in patients with atrial fibrillation (AF) to decide about the best anti-thrombotic medication (Table-2A,2B). Higher CHADS2 score translates into higher risk of stroke proportionately. Warfarin was the only agent available at the time of this tool’s development. There are now at least 3 newer anticoagulants which may have separate risk profile after we have head-to-head comparison. CHADS2 scoring system is for clinical practice and many other factors like
patient’s bleeding risk, preferences, individual comorbidities, tolerability etc. does affect the choice of one or another drug or to use it at all.

### Oral anticoagulants

After warfarin was approved for medical use in 1954, it remained the only oral anticoagulant for long-term prevention of thromboembolic disease until about two years ago when Federal Drug Administration (FDA) stamped dabigatran. Warfarin although reduces the stroke risk in AF patients by up to one-third compared to anti-platelets, it is, however, associated with excess haemorrhagic strokes and other major and minor bleedings. Use of warfarin is also riddled with various clinically concerning issues like need to monitor International normalised ratio (INR) on a regular basis, certain dietary restriction, genetic variability in drug metabolism and major drug interactions. So it was obvious that we needed drugs that could potentially circumvent the disadvantages of warfarin (Table-3).

### Newer anticoagulants

#### Direct Thrombin Inhibitors

Direct Thrombin Inhibitors (DTI) are specific thrombin inhibitors that inhibit both free and bound forms of thrombin. It is also said to reduce thrombin generation and inhibit platelet activation (Figure). These multiple effects on the coagulation cascade gives them better efficacy compared to parenteral counterparts. Ximelagatran was the first such DTI developed and tested, but was later withdrawn from the market because of potential hepatotoxicity. The second agent in this category, dabigatranetexilate, was tested later.
**DabigatranEtexilate**

Dabigatranetexilate is a pro-drug, which gets converted into dabigatran after absorption. Because its bioavailability is only 6%, its effective dose is as high as 150mg twice daily. A common side effect of it is dyspepsia that is attributed to the tartaric acid ingredient, which helps in dissolution and absorption from the intestine. FDA has approved 150mg bis in die (BID) of dabigatran for stroke prevention with normal renal function. But it recommends 75 mg BID if CrCl 15-50. Majority (80%) of the drug is metabolised through the kidneys and the liver clears the rest although it does not involve cytochrome P450 system.

The major trial that led to the approval of this drug was the Randomised trial of Long-term Anticoagulation Therapy (RE-LY) trial which enrolled 18,133 patients with NVAF. They compared 110mg and 150mg of dabigatran to warfarin (INR 2-3). The 110mg BID dose was non-inferior to warfarin and associated with lesser incidence of major haemorrhage, but 150mg BID dose was superior with similar risk of major haemorrhage. Major advantages of this drug cited are lack of need for routine monitoring, fewer drug interactions and dietary restriction. It has become a class IB recommendation in American Heart Association (AHA) and American College of Cardiology (ACC) guidelines for stroke prevention. The 2012 guideline of American College of Chest Physicians (ACCP) suggested that dabigatran should be selected as the drug of choice for stroke prevention in NVAF.

<table>
<thead>
<tr>
<th>Target Dosing</th>
<th>Warfarin (Coumadin)</th>
<th>DabigatranEtexilate (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-life</strong></td>
<td>40 hours</td>
<td>12-14 hours</td>
<td>7-11 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>None</td>
<td>80%</td>
<td>66% (33% unchanged, 33% active metabolite)</td>
<td>25% unchanged</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>No</td>
<td>Yes, 49-68% at 4 hours</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Routine monitoring</strong></td>
<td>INR</td>
<td>No (? pill count)</td>
<td>No (? Pill count)</td>
<td>No (pill count)</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Yes, Vitamin K</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug interaction</strong></td>
<td>Multiple</td>
<td>Potent inhibitor of P-gp</td>
<td>Potent inhibitor of CYP3A45</td>
<td>Potent inhibitor of CYP3A45</td>
</tr>
<tr>
<td><strong>CHADS2 score of patients studies</strong></td>
<td>&gt;1</td>
<td>Mean 2.1</td>
<td>Mean 3.5</td>
<td>Mean 2.1</td>
</tr>
<tr>
<td><strong>Patient populations not adequately studied</strong></td>
<td>BMI &gt;35, CrCl&lt;70</td>
<td>BMI &gt;35</td>
<td>BMI &gt;35</td>
<td>BMI &gt;35</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$4 plus monitoring cost</td>
<td>75mg or 150 mg Pradaxa capsules (60) : $318</td>
<td>Xarelto 10 mg (30) : $300; Eliquis 2.5 mg and 5 mg (60) : $300</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison to warfarin</strong></td>
<td>-</td>
<td>Less intracranial bleed, ischemic strokes; More GI bleed, more MI</td>
<td>Non-inferior in stroke prevention; No significant difference in bleeding; Bleeding, adherence</td>
<td>Decrease all cause mortality; Decrease bleeding</td>
</tr>
<tr>
<td><strong>Major concern</strong></td>
<td>Bleeding, Drug interaction</td>
<td>Bleeding (GI), drug stability, Adherence</td>
<td>Bleeding, adherence</td>
<td>Adherence</td>
</tr>
</tbody>
</table>

*CHADS2: Congestive heart failure, Hypertension, Aging (>65), Diabetes, Stroke or TIA. P-gp: P-glycoprotein, CYP3A4: Cytochrome P450. Potent inhibitor of P-glycoprotein includes quinidine and amiodarone. Potent inhibitors of CYP3A4 and P-gp include azole antifungals (e.g. ketoconazole, itraconazole, Voriconazole, and posaconazole) and protease inhibitors such as ritonavir.

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**Factor Xa inhibitors**

Factor Xa is situated at the junction of the intrinsic and extrinsic coagulation pathway. These groups of drugs by reversibly binding to the active site of factor Xa inhibit generation of fibrin from fibrinogen. Rivaroxaban and apixaban are already approved for stroke prevention in NVAF in the United States. Other members of this group in development are Edoxaban, LY 517717, YM 150, betrixaban, eribaxaban and TAK 442.

**Rivaroxaban**

Bioavailability of rivaroxaban ranges between 60-80%. One-third of the drug is excreted unchanged from the kidneys, and remaining two-third is metabolised by the live cytochrome P450 enzyme system. The recommended dose of rivaroxaban is 20 mg daily with creatinine clearance (CrCl)>50ml/min and 15mg daily with CrCl between 15-30 ml/min.

The drug was evaluated for the prevention of stroke and systemic embolism in the Rivaroxaban versus Warfarin in Non-valvular AF (ROCKET-AF) trial. It was a randomised, double-blind, double-dummy, event-driven, non-inferiority comparison of rivaroxaban (20 mg/day, 15mg/day if CrCl 30-49 mL/min) with warfarin for stroke prevention in AF. In patients with AF, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. There was an increase in the rate of gastrointestinal bleeding in the rivaroxaban group. Rivaroxaban now has been approved in the US for stroke prevention in NVAF, Venous Thromboembolism (VTE) prophylaxis after knee and hip surgery, deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment.

**Apixaban**

Apixaban is an orally bioavailable, highly selective, and direct acting/reversible factor Xa inhibitor. It is not recommended in patients with severe renal (CrCl<15) or hepatic dysfunction. Recommended dosage is 2.5mg twice daily with or without food.

Apixaban was first compared with Aspirin (acetylsalicylic acid, or ASA) in patients with AF not suitable for warfarin in the AVERROES trial. Apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial haemorrhage. The ARISTOTLE trial compared apixaban with warfarin in patients with AF. In patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. There were statistically significant reductions in intracranial bleeding and haemorrhagic stroke.

**Left ventricular Dysfunction and anticoagulation**

Incidence of embolism after acute myocardial infarction (MI) is highest in the first 3 months. Earlier studies had found that benefits of addition of warfarin on aspirin might exceed harms in post-acute coronary syndrome patients. However, a meta-analysis of 10 randomised controlled trials later showed that oral anticoagulation does not reduce all-cause death or re-infarction in survivors of acute MI across a wide range of patients and intensity of therapy. Oral anticoagulation did reduce the incidence of stroke by 30%, independent of ASA therapy, suggesting different mechanisms of cardiac and cerebral protection from ischaemic events. It rather increased the rate of nonfatal major and minor bleeding. Even then, AHA guidelines (2011) recommended warfarin for those at high risk (large anterior MI, thrombus in left ventricle) for at least 3 months at moderate intensity and in addition to ASA (Class IIA). Anticoagulant therapy may be considered for patients with ST-segment Elevation Myocardial Infarction (STEMI) and anterior apical akinesis or dyskinesis (Class IIB). Chronic heart failure (CHF), in general, is the second most common cause of cardioembolic stroke after AF. However, the use of warfarin in addition to aspirin didn’t make overall difference on risk of stroke in the WARCEF trial.

**Patent Foramen Ovale (PFO)**

A PFO is a remnant of the foetal circulation and may be found in approximately 25% of adults. In approximately 30% of young survivors of stroke, no clear cause of stroke is identified despite a thorough evaluation. PFO is found on trans-oesophageal echocardiography in about half of these patients. Because of the several observational studies (including a meta-analysis) and case series that suggested benefit of mechanical closure over the medical management, the mechanical closure was widely adopted in many countries in European and North American countries with the off-label use of cardiovascular devices. Now, there has been surge in healthy and lively debate about the closure of the PFO in the last couple of years when the three randomised trials failed to demonstrate unequivocal benefits of PFO closure at least in intention-to-treat analysis. However, the observation from the previous studies did concur with the result of the PICSS study that there is no difference between warfarin and ASA in the medical management of PFO in patients with cryptogenic stroke (CS) to prevent recurrences.
Despite those three largely negative randomised clinical trials, the best management of patients with CS and PFO still remains unsolved. In the CLOSURE I trial, at 2 years, there was no significant difference between the two treatment groups in the rate of recurrent stroke or TIA. Of note was the fact that closure of the PFO increased the risks of major vascular events and of AF.

Then, there came two other randomised trials published in the same issue of New England Journal of Medicine. In the RESPECT trial, the patients who had had a cryptogenic ischaemic stroke, closure of a PFO with the Amplatzer PFO Occluder was compared with medical therapy alone. No significant benefit of closure of the PFO was shown in the primary (intention-to-treat) analysis. However, closure of a PFO with the Amplatzer PFO Occluder was superior to medical therapy alone in the pre-specified per-protocol and as-treated analyses, with a low rate of associated risks. An exploratory subgroup analysis suggested heterogeneity of the treatment effect in favour of closure in subgroups defined according to two baseline characteristics: the presence of an atrial septal aneurysm and a substantial shunt size. The Amplatzer PFO Occluder, as compared with the STARFlex device used in CLOSURE I, was associated with higher effective closure rates, without provoking events that could lead to recurrent stroke, such as device thrombosis and AF.

In the PC trial, closure of PFO with the Amplatzer PFO Occluder for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of embolic events or death, as compared with medical therapy alone. There were fewer strokes in the closure group, but overall, few patients had a stroke and the difference was not significant. At a mean period of follow-up of 4 years, the event rates in both device and medical groups were much lower than expected which lowered the power of the trial significantly. Although the controversy over efficacy may not be settled, but it is worth noting that the safety profile for the Amplatzer device appeared to be superior to that of the STARFlex device tested in CLOSURE I. The incidence of clinical AF was increased by a factor of 10 in the closure group compared to the medically treated cohort in CLOSURE I and by a factor of only 2 to 3 in RESPECT and the PC Trial.

The 2012 American College of Chest Physicians (ACCP) guidelines recommend antiplatelet therapy for patients with cryptogenic ischaemic stroke and a PFO, and state that anti-coagulation is not indicated. These guidelines recommend ASA over no ASA for patients with CS and PFO or atrial septal aneurysm (ASA). For patients who experience recurrent events despite ASA therapy, the ACCP guidelines suggest treatment with vitamin K antagonist therapy and consideration of device closure over ASA. For patients with CS and PFO who have evidence of DVT, the ACCP guidelines recommend vitamin K antagonist therapy for 3 months and consideration of device closure over no vitamin K antagonist therapy or ASA therapy. The 2011 American Heart Association/American Stroke Association (AHA/ASA) guidelines state that antiplatelet therapy is reasonable for patients with an ischaemic stroke or TIA and a PFO, and that oral anticoagulation is reasonable for high-risk patients who have other indications such as a hypercoaguable state.

**Antiplatelets**

The efficacy of ASA was first tested in a scientific study (US Aspirin trial) in 1977 for prevention of recurrent ischaemic stroke. Since then large number of trials have been performed using ASA monotherapy versus placebo, warfarin or heparin in non-cardioembolic ischaemic strokes. All of these trials demonstrated ASA as effective or at least non-inferior to its counterpart in those individual trials. It is often a common treatment practice to use warfarin and ASA or other antiplatelet in the setting of AF and coronary artery disease (CAD). However, there is not only negative or inconclusive data, but both major and non-major bleeding risk is significantly high without added benefit of ischaemic stroke prevention. The use of ASA for cardiovascular (including but not specific to stroke) prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%) (Class I; Level of Evidence A).

ASA (81mg daily or 100mg every other day) can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (Class IIa; Level of Evidence B). ASA is not useful for preventing a first stroke in persons at low risk (Class III; Level of Evidence A).

ASA is also not useful for preventing a first stroke in persons with diabetes or diabetes plus asymptomatic peripheral artery disease (defined as an ankle brachial pressure index 0.99) in the absence of other established cardiovascular diseases (CVD) (Class III; Level of Evidence B).

On the other hand, 20-year follow-up study of various randomised trial participants of low-dose ASA trials demonstrated that the addition of low-dose ASA is efficacious in preventing proximal colorectal cancer,
indicating that the use of ASA may have benefits beyond that of primary prevention of CVD.\textsuperscript{21}

Another antiplatelet agent, clopidogrel, has been tested against ASA, placebo or with combination in various trials. Clopidogrel was found slightly superior to ASA in the randomised, blinded, trial of clopidogrel versus ASA in patients at risk of ischaemic events (CAPRIE) trial.\textsuperscript{22} However, combination of clopidogrel and ASA was found to be no better than ASA or clopidogrel monotherapy (MATCH trial;\textsuperscript{23} CHARISMA trial;\textsuperscript{24} SPS3 trial).\textsuperscript{25} The latest of these trials was SPS3 which enrolled subjects with MRI-proven small subcortical (“lacunar”) infarcts within six months of the index event to daily ASA 325mg/placebo vs. ASA 325mg/clopidogrel 75mg and more aggressive (<130 mmHg) vs. less aggressive (130-149 mmHg) systolic blood pressure targets. There was no significant difference in overall risk of recurrent stroke between the single vs. dual antiplatelet groups. In the PRoFESS trial, clopidogrel was found to be roughly equivalent to combination of ASA and dipyridamole.\textsuperscript{26} Idea of combining ASA and clopidogrel in stroke prevention comes from the experience with the use of these agents in coronary artery diseases. Unfortunately this could not get translated into the stroke arena. The interest in pursuing dual antiplatelets didn’t die off despite the early disappointing results. The prematurely terminated FASTER trial, which compared combination ASA and clopidogrel with loading dose to ASA within 24h of TIA or minor stroke, suggested that very early dual therapy might reduce early stroke recurrence.\textsuperscript{27} The CHANCE trial from China recruited patients with TIA or minor stroke that can be treated within 24 hours after the onset of symptoms. The combination of clopidogrel and ASA is superior to ASA alone for reducing the risk of stroke in the first 90 days and does not increase the risk of haemorrhage.\textsuperscript{28}

There are a number of trials assessing the efficacy of dual antiplatelets in acute stroke settings. The Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke (POINT) trial is enrolling patients in North America and Europe. Investigators plan to randomise 4,200 participants to ASA/clopidogrel or ASA alone within 12 hours after minor stroke or TIA and assessing vascular event rate at 90 days (NCT00991029). The recently completed combination of clopidogrel and ASA for Prevention of Early Recurrence in Acute Atherothrombotic Stroke (COMPRESS) study is assessing whether ASA plus clopidogrel vs. ASA alone within 48 hours of stroke will help to reduce new diffusion-weighted lesions on magnetic resonance imaging (MRI) at 30 days (NCT00814268). The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial is enrolling patients within 48 hours of non-cardioembolic ischaemic events to ASA/dipyridamole/clopidogrel vs. ASA/dipyridamole and assessing stroke severity at 90 days as the primary outcome and recurrent stroke amongst the secondary outcomes (NCT01661322).

Stroke or TIA from the extra-cranial or intracranial large vessel disease has the highest chance of early recurrence. Carotid endarterectomy and stenting are superior to best medical therapy alone (including antiplatelet therapy) for secondary prevention for symptomatic extra-cranial carotid stenosis. Treatment of intracranial large vessel atherosclerosis has been difficult to treat. It’s now known that extra-cranial-intracranial bypass, dose-adjusted warfarin or stenting do not fare better than best medical therapy that includes antiplatelets. In a much debated trial, SAMMPRIS trial,\textsuperscript{29} among patients with intracranial arterial stenosis (70 to 99%), aggressive medical management was superior to Percutaneous Transluminal Angioplasty and Stenting (PTAS) with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected. Aggressive medical management consisted of ASA, at a dose of 325mg per day; clopidogrel, at a dose of 75mg per day for 90 days after enrollment and management of the primary and secondary risk factors with the help of a lifestyle modification programme.

**Non-pharmacological treatment of AF**

Despite the advancements in medical therapy, oral anticoagulants do not lower the risk of stroke to zero. Major bleeding, physician and patient reluctance to use anticoagulants, and patient non-compliance limit use of oral anticoagulants. Therefore, the idea of non-pharmacological methods of reducing stroke is very attractive.

**Eradication of AF**

Currently there is no data to support that either catheter ablation or the Maze procedure reduces the risk of early or late stroke. Patients frequently have paroxysmal AF even after the procedure. Patients who undergo above procedures should still be on oral anticoagulant. Currently, the 2012 Heart Rhythm Society (HRS) guidelines recommend consideration for surgical ablation of AF only in symptomatic AF patients undergoing other cardiac surgery.\textsuperscript{30}

**Left Atrial Appendage (LAA) Closure**

With the LAA being a dominant source of thrombus in AF,
it is plausible that its occlusion will lead to a decreased risk of stroke in patients with AF. To date, the strongest recommendation comes from the European Society of Cardiology (ESC),\(^1\) which recommends LAA occlusion for patients with AF undergoing mitral valve surgery (Level of Evidence C, Class IIb). In addition, the ESC also recommends that percutaneous LAA closure be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulant administration (Level of Evidence B, Class IIb).

Isolation of LAA from the systemic circulation would theoretically prevent all the clots dislodging into the main stream. One of the devices that are being used is the WATCHMAN device, which is an expandable device, deployed in the LAA via a trans-septal catheter. The WATCHMAN device was evaluated in the PROTECT AF non-inferiority trial in which over 700 patients with nonvalvular AF were randomly assigned in a 2:1 ratio to either the device or to long-term warfarin\(^2\) (INR 2.0 to 3.0). The efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. LAA closure lowered risk of the composite of stroke, cardiovascular cause of death, or systemic embolism by 40% over the anticoagulant alone at 4 years, which met statistical criteria for superiority.\(^3\) Quality of life has been found to be better in patients with device closure than in those treated with warfarin. However, in the newer PREVAIL trial\(^4\) with the device, efficacy endpoints met non-inferiority at best. Safety has come out worse or non-inferior for WATCHMAN versus continued warfarin in the trials. The device is also a reasonable alternative to patients who otherwise cannot tolerate anticoagulants. WATCHMAN devices and several others (The LARIAT, Amplatzer) are being further evaluated and have not been cleared by the FDA for general use yet.

**Conclusion**

All patients with NVAF and CHADS2 score of more than 1 should receive antithrombotic therapy. Warfarin, Dabigatran, rivaroxaban, and apixaban currently carry FDA approval for stroke and systemic embolism prevention in AF. The new oral anticoagulants have been found to be as efficacious as warfarin (if not better) and safer in terms of intracranial bleeding. The most salient feature of all these newer oral anticoagulants is the impressive reduction in the risk of cerebral haemorrhage and other intracranial bleeds compared to warfarin. This is highly relevant clinically because the mortality of anticoagulation-associated cerebral haemorrhage is around 40%. The available evidence does not support the mechanical closure of PFO for prevention of recurrence CS though some scholars still argue there is a room for more research. Dual antiplatelet therapy was found to be effective for prevention of early recurrent strokes in the CHANCE trial, but there is no data supporting its long-term use. Aggressive medical therapy is still the mainstay of treatment of strokes secondary to intracranial atherosclerosis.

**References**


