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Ischemic Stroke: Risk Stratification, Warfarin Teatment and Outcome Measure

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Abstract

Stroke is a focal neurological syndrome of vascular basis, which may be due to ischemic thrombo-embolism or intra-cerebral haemorrhage. This condition has to be treated on emergency basis as it may cause an irreversible neurological damage. Warfarin has been a widely used oral anti-coagulant in treating ischemic stroke patients. This review highlights the benefits and challenges of warfarin treatment in stroke patients and discusses about the importance of risk stratification scores & bleeding scores in estimating the bleeding risk associated with warfarin treatment. This review also highlights the use of stroke outcome measures in identifying the patients with post-stroke disabilities to provide patient specific treatment.

Introduction

Stroke is a focal neurological syndrome, which is characterised by acute neurological deficit that may be due to arterial occlusion or intra-cerebral haemorrhage. 85 to 95% of strokes are ischemic and 10-15% is due to intra-cerebral haemorrhage (ICH) (Muir 2013). Based on duration four neurological phenomena have been defined for stroke: TIA (Transient ischemic attack), reversible ischemic neurological deficit (RIND), stroke in evolution, and Completed stroke. TIA is also called as mini stroke as it is a localized transient brain ischemia, which is sudden, and can be reversible within 24 hours. RIND is a neurological impairment, which can take more than 24 hours time to recover. Stroke in evolution can be defined as the symptoms associated to it only worsen over time. A completed stroke can be defined as a condition in which neurological signs and symptoms remain stable for more than 24 hours (Fatahzadeh & Glick 2006).

Epidemiology

Stroke is the third major cause of death in United States, Europe, and most parts of the world. Worldwide stroke accounts for approximately 5.5 million deaths annually and major cause for disabilities. Approximately 150,000 incidences of strokes take place annually in UK alone (Muir 2013). It has been a disease of aging population older than 65 years and every year the population of this age continuing to increase by 9 million per year. By 2025, the worldwide population of people aged more than 65 years is estimated to be approximately 800 million that shows us the risk and economic impact of this problem on the world (Mukherjee & Patil 2011).

Key Words:
Stroke, Ischemic Stroke, Risk Stratification Schemes, Stroke Outcomes, Stroke Outcome Measures, Warfarin Treatment.

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None.

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Classification

Stroke can be classified based on the Oxfordshire Community Stroke Project (OCSP). It has been the standard classification in categorising the acute ischemic stroke patients based on the occlusion and the part of the brain which would be affected. Different types of clinical features would depend on the major intra-cranial arteries that are affected by the occlusion and the portion of brain that has been affected. OCSP classifies infracts based on their location in the intra- cranial arteries.

OCSP classification:

1. Total anterior circulation infracts (TACI)
2. Partial anterior circulation infracts (PACI)
3. Posterior circulation infracts (POCI) and
4. Lacunar infracts (LACI) (Sean J. Pittock).

Patients can be classified to be with TACI if they are with a combination of higher cerebral dysfunction, homonymous visual field defect, and sensory deficit at two areas of face, arm and leg. Patients with PACI can be classified if the patients have any two components of TACI or higher cerebral dysfunction. Patients are considered to have LACI if there is a pure motor or sensory stroke, sensori-motor stroke, and ataxic hemiparesis. Patients with a posterior circulatory dysfunction and ipsilateral cranial nerve palsy with motor and sensory deficit are considered to have POCI (Li et al. 2003).

Risk Factors

There has been a great deal of investigating different risk factors

Table 1: Risk factors for stroke

Risk Factors	Reference
Age	Marinigh et al. 2010, Bentsen et al. 2014
Gender	Koton et al. 2013, Nolte et al. 2005
Diabetes	Béjot & Giroud 2010, Kaarisalo et al. 2005
Smoking	Edjoc et al. 2013, Tse et al. 2012
Hypertension	Mancia 2004, Dahlöf 2007, Gorgui et al. 2014
Coronary Heart disease	Iwasaki et al. 2014
Atrial Fibrillation	Bansil & Karim 2004, Mizrahi et al. 2014

that increase the incidence of the stroke and these have been summarized in Table 1. A major factor that increases the occurrence of stroke is atrial fibrillation. Atrial fibrillation (AF) increases the risk of stroke and thromboembolism by 5 folds and considered as a major risk factor (Jover et al. 2012).

Atrial Fibrillation (AF)

Atrial fibrillation is a clinically encountered arrhythmia and encompasses lone atrial fibrillation to paroxysmal AF to chronic atrial fibrillation. Atrial fibrillation is mostly associated with heart failure, aging and diseases related to aging (Mathew et al. 2009). Atrial fibrillation has been associated with cardio embolic stroke, which can be neurologically devastating (del Conde & Halperin 2013). The major clinical feature of AF is a decrease in atrial contractility and increased atrial compliance, which leads to mechanical remodelling of the heart. This leads to stretching in the atrial myocardium and this atrial remodelling increase the atrial fibrosis and decreases the conduction velocity, which also shortens the refractory period in atria (Mathew et al. 2009). AF is also caused due to an irregular and increased conduction of impulses in atrial part of the heart. AF reduces the flow velocity of the left atria and causes delayed emptying from the atria which leads to thrombus formation. Strokes caused by AF have higher fatality when compared to other risk factors due to the formation of large thrombi in the atria which may occludes in the cerebral arteries causing infarction and stroke (Alberts et al. 2012).

Risk Stratification Schemes

There are two risk stratification scores for stroke and thromboembolism, which are mostly used to assess the risk of stroke in patients with non-valvular atrial fibrillation. The two schemes, which are in use, are CHADS2 scheme and CHA2DS2-VAScscheme. Both the schemes have been summarized in table 2 & 3.

CHADS2 Score

The US practise guidelines recommended the use of CHADS2 score (assigns score for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, transient ischemic attack or prior occurrence of stroke). This scheme assesses different risk factors and most important of those are the age and prior stroke. It assigns a score for each risk factor with '1' except prior stroke which is assigned '2' which makes up score '6' in total (Poli et al. 2007). The patients with a score of 6 showed an increase of 2.5 to 2.7 folds in the hospitalization risk due to stroke (Naccarelli et al. 2012). Pre-admission CHADS2 score relates to the severity and stroke outcomes in patients with atrial fibrillation (Sato et al. 2011).

CHA2DS2-VASc Score

The European guidelines recommended the use of a new risk stratification scheme called CHA2DS2-VASc scheme, which was superior to the CHADS2 scheme as it also assesses additional risk factors that were previously underestimated. CHA2DS2-VASc score (assigns score for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, transient ischemic attack or prior stroke – vascular disease, age 65-74 years, sex (female)) is used to assess all the possible risk factors, and scores them '1' for all the factors except age≥75 years and prior stroke which are given '2' where, the maximum score is '9' (Chao et al. 2011).

This scheme assesses additional risk factors such as vascular diseases such as myocardial infarction, peripheral artery disease, and complex aortic plaque. The patients with a score of '9' show an increase of 3.0 folds in the hospitalisation risk due to severity of the condition (Naccarelli et al. 2012). The CHA2DS2-VASc scheme is more advantageous when compared to CHADS2 scheme as it also assesses additional risk factors and is also useful in identifying patients who despite having a CHADS2 score of '0', still have a high risk of stroke and can be prescribed anticoagulants. It is also used to identify the patients who will truly benefit from the antithrombotic agents and also who are at low risk of stroke with a CHA2DS2-VASc score equal to '0' (del Conde & Halperin 2013). The score '2' in both the schemes recommends the use of anti-platelet or anticoagulant therapy. The score '1' which is risk factor specific can also be considered for anti-coagulant therapy according to the recent guidelines. In both scoring systems Age and prior stroke are considered as major risk factors (Wadke 2013).

Warfarin

Mechanism of Action

Warfarin is a vitamin K antagonist, which has an inhibitory effect on the vitamin K cycle which in-turn inhibits the vitamin K dependent coagulation factors II, VII, IX and X. Warfarin inhibits the synthesis of vitamin K dependent coagulation factors (II, VII, IX, X, protein C and protein S) by inhibiting the γ-carboxylation of glutamate residues of these clotting factors, which ultimately inhibits them to bind with Calcium. The principle mechanism behind the anti-coagulant effect of warfarin is that it inhibits the reduction of oxidized vitamin K which is essential for the activation of clotting factors by carboxylation. This inhibits the formation of functionally active prothrombinase complex, thrombin and fibrin which, ultimately gives an anti-coagulant effect. The figure 1 shows us the coagulation pathway and inhibitory effect of warfarin (Riley et al. 2000). Warfarin is mainly used to prevent venous thromboembolism and systemic embolism in patients with atrial fibrillation or prosthetic heart valves (Eriksson & Wadelius 2012).

Pharmacokinetics

Warfarin is a highly plasma bound drug which is completely absorbed from the upper intestinal tract and reaches peak plasma level in one hour. It is 98-99% plasma bound and has a half-life of 40 hours. Warfarin is metabolised by microsomal hepatic enzymes and

Table 2: CHADS2 Scheme

CHADS2 Acronym	Score
Congestive heart failure	1
Hypertension	1
Age≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6

converted into hydroxylated inactive metabolites which, undergo conjugation with glucuronic acid and the conjugates are excreted in urine and faeces (Riley et al. 2000).

International Normalization Ratio (INR) & Anti-Coagulation

According to WHO guidelines, INR has been defined as, 'For a given plasma or whole blood specimen from a patient on long-term oral anticoagulant therapy, a value calculated from the prothrombin-time ratio using a prothrombin-time system with a known ISI (international sensitivity index) according to the formula INR = (PT/MNPT)ISI.' Determination of INR is mandatory for the controlled use of oral anti-coagulants (van den Besselaar et al. 2004). INR has been a great form of TDM (Therapeutic drug monitoring) in the patients who are on warfarin. The British Society of Haematology and the American college of Chest Physicians recommend a therapeutic range of INR as 2-3. It has been observed that an increase in INR more than 4.5 has shown an exponential increase in the risk of bleeding. The monitoring should start from second and third dose which should be continued until the INR reaches an optimal level and this frequency can be reduced when the stable dose administration is achieved (Hu et al. 2012).

Warfarin Treatment- Risks and Benefits

Benefits

Warfarin is a potent anti-coagulant and it has been shown that it can cause a great decrease in the risk of stroke when compared to other anti-coagulant drugs. In a meta-analysis warfarin decreased the risk of stroke by 64% when compared to placebo and 40% when compared to anti-platelet drugs (Deedwania 2013).

Practical Issues

There are many practical issues in usage of warfarin as anti-coagulant. The guidelines recommend the regular monitoring of INR values and the optimal INR which should be maintained would be 2.0-3.0 to obtain an optimal anti-coagulant effect and minimize the risk of bleeding. However, it is a very hard task to maintain the INR range as it is affected by drug-drug interactions, drug-food interaction and genotype variation. Age has been the most important factor that has great effect on INR value. So, estimation of INR on regular basis and dose adjustment has been a major drawback in the usage of warfarin (Deedwania 2013).

Drug Interactions

Drug interactions can alter the anti-coagulation effect of warfarin and that can lead to over or under-coagulation effect. Warfarin has two isomers and the enzymes responsible for their metabolic elimination are different. (S)-warfarin is eliminated by enzyme CYP2C9 and (R)- warfarin eliminated by CYP1A1/CYP1A2/CYP3A4. The drugs which, induce these enzymes can cause an increased elimination of warfarin (e.g.Carbamazepine, phenytoin, and rifampicin) and the drugs which inhibit these enzymes will in turn inhibit the elimination of warfarin and increases the anti-coagulant effect (e.g. amiodarone) (Eriksson & Wadelius 2012). Most of the corticosteroids, cimetidine, omeprazole, thyroxine, and allopurinol enhance the anti-coagulant action of warfarin (Shannon 2007).

Effect of Dietary Intake

Vitamin K containing food causes variability in the efficacy of warfarin as it is responsible for the production of coagulation factors. Vitamin K is present in different green vegetables such as broccoli, sprouts and spinach. There have been studies showing that an intake of 100µg of vitamin K for 4 consecutive days can lower the INR by 0.2. So, it is recommended for the patient to have a regular intake so the accurate INR can be calculated and the adjustment of dose can be carried out (Eriksson & Wadelius 2012).

Table 3: CHA2DS2-VASc Scheme

CHA2 DS2-VASc Acronym	Score
Congestive heart failure/ Left ventricular dysfunction	1
Hypertension	1
Age≥75 years	2
Diabetes mellitus	1
Stroke/TIE/TE	2
Vascular disease	1
Age (65-74 years)	1
Sex (female gender)	1
Maximum	9

Genetic Factor

Individuals have a different level of sensitivity according to the genetic variation. A mutation in the gene VKORC1 that encodes the vitamin K epoxide reductase, an enzyme which is the major target for warfarin can cause increased resistance to warfarin. It has been also found that genetic variation in CYP2C9 showed impaired metabolism of warfarin. Therefore, these two genes have been the genetic determinants of warfarin dose (Yang et al. 2013) (Supe et al. 2014).

Bleeding Risk

The bleeding risks can be of three types:

Intracranial Haemorrhage: The risk of intracranial haemorrhage is very less when compared with the benefits of using warfarin. Intracranial haemorrhage mostly occurs in patients who are older than 75 years and with uncontrolled hypertension which is usually more than 160mm Hg systolic blood pressure and prior stroke.

Extra-cranial Haemorrhage: The risk of extra-cranial haemorrhage is very low significant and less life threatening when compared to intracranial haemorrhage. Falls: The risk of bleeding after falls is very low and is considered of less importance when it is weighed against the benefits of warfarin (del Conde & Halperin 2013).

Bleeding Risk Schemes

The major adverse effect in the usage of anti-coagulants is bleeding and for the patients who are on anticoagulants and with an INR scores of more than 5.0 the risk of bleeding increases exponentially (Shannon 2007). There are different types of bleeding scores which have been developed to estimate the bleeding risk for individual patient and they are:

HAS-BLED Score

European guidelines recommended a bleeding risk score which is called the HAS-BLED score (assigns score to hypertension, abnormal renal/liver function, stroke – bleeding history, labile international normalization ratio, elderly (Age>65 years), and drugs/alcohol concomitantly) which is calculated as 1 point for each factor with a maximum score of 7 (Kiviniemi et al. 2014). This score is used to assess the bleeding risk in atrial fibrillation patients. The patients with HAS-BLED score 0-2 have low risk of bleeding and with more than 3 have high risk of bleeding which should be treated by reversing the anticoagulant effect and by maintaining the INR by dose adjustments (Lip 2011).

HEMORR2HAGES Scheme

It is a bleeding score, which is the only score that includes the

Table 4: Modified Rankin Scale

Scale	Modified Rankin Scale (mRs)
0	no symptoms
1	No significant disability able to perform all usual duties and activities
2	slight disability able to look after own affairs without assistance
3	moderate disability Requires some help, but able to walk without assistance
4	moderately severe disability Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability Bedridden, incontinent, and requires constant nursing care and attention.
6	Dead

genetic factors. HEMORR2HAGES scheme (assigns points for hepatic or renal disease, ethanol abuse, malignancy, older age (greater than 75), reduced platelet count or function, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factor, excessive fall risk, and stroke) is used to assess different risk factors and scores one for all the risk factors except re-bleeding risk which is scored two points (del Conde & Halperin 2013). This is the only scoring system, which considers genetic factors (CYP2C9), excessive fall and stroke (Alberts et al. 2012).

Measuring Stroke Severity

NIHSS (National Institutes of Health Stroke Scale)

Stroke severity can be measured using a severity scale, the National Institutes of Health Stroke Scale (NIHSS) that includes 15 item scales that include assessment of motor function and sensory function, level of consciousness and orientation. It ranges from 0 to 34 where if the patient score is below 10 they are likely to have a favourable outcome after 1 year when compared to patients with a score of more than 20. Patients with severe stroke and with a score of more than 22 have poor prognosis (Institutes et al. 2009). NIHSS shows a high accuracy of prediction of ADL (activities of daily living) dependency by the patients post-stroke (Kwakkel et al. 2010).

Measuring Outcomes After Stroke

The outcomes after stroke can be measured using different neurological and disability rating scales.

Table 5: Glasgow Coma Scale

Glasgow Coma Scale		
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal response	Orientated	5
	Confused conversation	4
	Words (inappropriate)	3
	Sounds (incomprehensible)	2
	None	1
Best motor response	Obey commands	6
	Localize pain	5
	Flexion Normal	4
	Abnormal	3
	Extend	2
	None	1
Total Coma score		3/15 15/15

The Modified Rankin Scale

The modified Rankin scale has been devised to assess the disability after stroke. It is a measure of functional independence, which incorporates the WHO components such as body function, activities and participations. A patient using adaptive but still does not need any assistance is considered independent and a patient who takes aid of another person is considered dependent (Kasner 2006). This scale ranges from 0 to 6 where 0 indicates no symptoms; and 1-2 indicates mild disability; 3 shows moderate disability; and 4 to 5 show severe disability and 6 is death. This shows favourable out-come with a score of 0-1 and unfavourable score of 2-6. Table 4 shows Modified Rankin Scale in detail (Institutes et al. 2009). It has been shown that modified rankin scale can be used to study the quality of life in stroke survivors (Singhpoo et al. 2012).

Glasgow Coma Scale

Glasgow coma scale has been a simple measure of conscious level and this scale has been widely accepted by Neurological units in most of the English speaking countries. It has been a cumulative measure of arousal, awareness, and activity, which have been termed as eye opening response, best verbal response and best motor response. The maximum score calculated is 15 and this is further categorised in as minor (GCS ≥ 13), moderate (GCS 9–12), and severe injury (GCS<9). The components of GCS are better described in Table 5 (Barlow 2012) (Matis & Birbilis 2008).

Barthel Index (BI)

BI is a scale, which consists of 10 items that measure the function in terms of activities such as, daily living and mobility. The scale ranges from 0 to 100 the higher the score, more the patient is independent. The score 100 indicates that he is independent in feeding, dressing, getting in & out of bed, bathing, can walk at least one block; and can ascend and descend stairs without help (Katz for the Association of Rheumat 2003). A study investigating the accuracy of Barthel Index revealed good discriminative properties at 6 months post-stroke (Kwakkel et al. 2011).

Six Simple-Variable (SSV) Model

Six simple variable model has been developed in Oxfordshire Community Stroke Project (OSCP) to predict the survival free of dependency (modified Rankin scale <3) (Dennis 2008). SSV model is useful in measuring the dependency and death in stroke patients. This model includes six different variables such as age, verbal component of Glasgow coma scale (GCS), and arm power, ability to walk, pre-stroke living condition and pre-stroke dependency (Institutes et al. 2009). SSV model predicts the outcome of stroke patients with cerebral infracts with a great precision (Li et al. 2012).

Conclusion

Both the risk stratification and bleeding scores carry valuable information of the stroke patients. Treatment with warfarin can be decided on the basis of pre-admission CHADS2 and CHA2DS2-VASc scores of the patients. The bleeding scores and regular monitoring of INR values are helpful in preventing bleeding risk associated with warfarin. Better understanding of stroke outcome measures would be helpful in treating the patient according to their post-stroke disabilities.

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