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# RISK EVALUATION OF THROMBO-EMBOLISM DURING STROKE IN ASIAN PATIENTS: NEED FOR PHARMACOLOGICAL THROMBOPROPHYLAXIS

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## ABSTRACT

Venous thrombo-embolism (VTE) is one of the serious complications in stroke patients. Early diagnosis and proper treatment are warranted to mitigate morbidity and mortality. Epidemiological evidence available so far favours much lower risk of VTE among Asians. Pharmacological management against VTE is highly effective but it is expensive and increases the chances of bleeding. Can the antithrombotic treatment be recommended as a prophylaxis against VTE among Asian population or we have cheaper, effective, and safer options available? Nonpharmacological treatment to prevent the incidence of VTE include graduated compression stockings, intermittent pneumatic compressions and early mobilization. Putting these options into action without pharmacological treatment may prove sufficient and effective without risking the patients to suffer from bleeding complications, particularly in cases where the severity of illness and chances of VTE are low. In such cases, non-pharmacological prophylaxis may prove more cost effective. This will improve the quality of care in regions where most of the healthcare expenses are managed through out-of-pocket spending.

**Keywords:** Stroke; Thromboembolism; Prophylaxis; Asian

## INTRODUCTION

Stroke is one of the leading cause of disability and death across the globe, adding to the sufferings of people in developing countries.<sup>1</sup> Every 4 minutes, someone dies of stroke in the United States while one in 6 deaths is attributed to stroke.<sup>2,3</sup> During early stages at the hospital, stroke patients may suffer a number of complications which can ultimately determine the patients' outcome. These complications include swallowing difficulty, aspiration pneumonia, urinary incontinence, urinary tract infection, deep venous thrombosis, pulmonary embolism, pressure sores, seizures, depression, and constipation.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are considered to be among the common complications during stroke. Risk factors predispose stroke sufferers to develop these complications in addition to the general risk factors for thrombo-embolism. Immobility, limbs' paralysis, increased prothrombotic activities during stroke all add to increasing the risk of thrombosis.<sup>4</sup> General risk factors increasing the chances of DVT incidence include obesity, female gender, old age, active cancer, hormone replacement therapy,

thrombophilia, genetic predisposition and ethnicity.<sup>5</sup> The most common cause of death from a DVT in stroke sufferers is a pulmonary embolism.<sup>6-8</sup> Institution of prophylactic anticoagulant therapy is recommended to prevent the DVT. Early anticoagulation does decrease the occurrence of pulmonary embolism but at the expense of a rise in haemorrhage related complications.<sup>9,10</sup> A number of studies in Asian population (as opposed to the Caucasian population) report much lower incidence of venous thrombo-embolism (VTE) in the general population as well as in stroke patients. This difference in its incidence has raised several questions: Does the current incidence rate of DVT in Asians represent a true disease burden; What are the factors/reasons behind this difference; Can we try alternative less expensive prophylactic methods in Asians with limited resources where most of the health expenses are managed by out-of-pocket spending?

## Incidence of deep venous thrombosis in Asians and the rest of the world (ROW)

Venous thrombo-embolism is a major health concern causing morbidity worldwide and placed on third number after myocardial infarction and stroke

as a cause of death in the west. Annually 100,000 to 180,000 patients die of VTE in the United States.<sup>11</sup> Deep venous thrombosis is a common complication following stroke. The incidence of VTE following stroke has been reported to be up to 75% and 80% depending upon the diagnostic tool and method of evaluation used.<sup>12,13</sup> Up to 80% of the DVTs that develop occurs within 10 days of stroke onset; most of them during 2-7 days of stroke.<sup>13</sup>

The VTE incidence reported in the literature among the Asian population has been much lower than the one reported above.<sup>14</sup> In a prospective study from China, the DVT (diagnosed with complete compression duplex ultrasonography performed at day 14 of stroke onset) incidence was 12.4% among stroke sufferers.<sup>4</sup> A systematic review conducted on the incidence of VTE in Asian populations reported its incidence to be 5 to 6 times lower than the western countries. Population wide annual VTE incidence reported in different Asian countries ranged from 8.8 to 19.9 per 100,000 (As opposed to 114-184 cases per 100,000 population in the west). The incidence of VTE in stroke patients remained less than 1%.<sup>15,16</sup> The highest annual incidence of VTE in general population of Korea recorded between 2009 and 2013 was 23.4 per 100,000 individuals.<sup>17</sup> Similarly the incidence of DVT (diagnosed through lower extremity doppler ultrasonography conducted within three days of admission) in stroke patients admitted to the Korean hospitals was between 5.8 to 13.1%.<sup>18</sup> The incidence reported among stroke survivors was 4.8% in a study from Singapore (through doppler ultrasound conducted within 48 hours of stroke to exclude pre-existing DVT and on a follow up scan after 7 days of admission).<sup>19</sup>

**Difference in incidence: The role of risk factors**

Several risk factors have been attributed to the development of DVT/VTE. A summary of the risks has been provided in the table 1.

The lower rate of DVT incidence in Asians has been linked most of the time due to technical reasons. Lack of diagnosis due to low disease awareness, lack of attention due to perceived low incidence, limited epidemiological studies, low autopsy rates due to cultural and religious reasons, asymptomatic disease and subsequent lack of seeking medical advice, paucity of trained staff to assess the patient properly has been considered to underestimate the actual disease burden.<sup>20-23</sup> Had that been the sole reasons, Asian population residing in the developed countries with proper access to the health facilities should have comparable incidence. But in a study conducted in Northern California, 61,459 volunteers participating between 1996-2015, 4674 patients were diagnosed with VTE during this period. Comparison among different ethnic groups found a much lower risk of VTE in Asians/Asian Americans as opposed to Whites. This lower rate of incidence suggests some inherent protection against VTE in Asians that may either be genetic or acquired.<sup>24-26</sup> One of the prominent facts that may explain these differences in incidence rates include a high prevalence of factor V Leiden deficiency, more common in Whites than Asians, making them susceptible to a hypercoagulable state and hence higher chances of venous thrombo-embolism. Similarly, lower fibrinogen, factor VIIc, factor VIIIc and prothrombin gene G20210A levels/prevalence cause this West-Asian disparity.<sup>24,25</sup> In addition, other general risk

factors: obesity, old age, cancer prevalence and the use of hormone replacement therapy are also higher in the west than in the Asian population, so it can be genuinely argued that there are sufficient reasons for a higher incidence among the western population.<sup>27</sup>

**Pharmacological thromboprophylaxis: Benefit versus Risk**

The risk of DVT is highly predictable during the first 14 days of stroke. Pharmacological prophylaxis does decrease the chances of VTE and subsequently a non-significant reduction in mortality but at the expense of haemorrhage related complications thus nullifying the benefits. The total bleeding episodes with VTE prophylaxis were 8% in PREVAIL study with up to 2 % of intracranial bleeding episodes reported.<sup>4,28</sup> A meta-analysis of 11 randomised controlled trials conducted on antithrombotic medications use in stroke patients reported a significant reduction in VTE with a significant rise in extracranial bleeding. The nonsignificant mortality reduction was offset by a nonsignificant rise in case fatality due to bleeding. The meta-analysis recommended against the use of antithrombotic medications routinely in stroke patients.<sup>29</sup>

**Mechanical vs pharmacological prophylaxis: The cost effectiveness**

Mechanical methods to prevent throm-

Table 1: Common risk factors causing DVT in stroke patients<sup>14,18,20</sup>

Stroke related risk factors	General risk factors for DVT/VTE
Immobility	Old age
High NIHSS score	Obesity
Lower limbs inability to move	Active cancer
Hemiparesis	Hormone replacement therapy
Receipt of tissue plasminogen activator	Thrombophilia
Previous history of stroke	Female gender
	Chronic inflammatory disorders
	Diabetes mellitus
	Transient provoking factors (e.g., Surgery, trauma, pregnancy)
	Family or past history of VTE

basis are considered equally effective to heparin with inherent quality of without increasing the risk of bleeding.<sup>30,31</sup> A study evaluating the add on benefit of mechanical prophylaxis to the pharmacological thromboprophylaxis reported 40-fold reduction in the VTE incidence among stroke patient.<sup>6</sup> So if the results are extrapolated in combination with other studies conducted, there is a clear benefit of mechanical thromboprophylaxis.

If the cost effectiveness of different modalities is taken into account, then intermittent pneumatic compression stockings stands as the cheapest prophylaxis method as reported in a study conducted in Australia.<sup>32</sup>

#### Out-of-pocket healthcare spending in Asia

Asians account for more than half of world's population but unfortunately, most of the Asian countries have poor healthcare system. Out of pocket expenditure in healthcare is higher in the low- and middle-income countries because inadequate healthcare resources don't suffice everyone to have adequate access to fulfil their health needs. People are forced to choose between fulfilling health or other necessities.<sup>33</sup> Having a poor socioeconomic background may be one of the reasons for spending on healthcare out of pocket, causing further financial implications and thus a vicious cycle ensues. Ultimately excessive out of pocket spending on healthcare may cause hindrance in receiving/providing optimal health care.<sup>34</sup> Based on this, can the same guidelines in the treatment of VTE/DVT for western population be translated for Asians if the risks/incidence doesn't match? On the analogy, "one size shoe doesn't fit everyone"; guidelines and treatment options may be modified based on the risk assessment evidence, safety measures, healthcare facilities, support available and cost effectiveness, particularly in regions where most of the health expenses are managed by patients themselves from their household consumption or income.

## CONCLUSION AND RECOMMENDATIONS

Data on reliably assessing the incidence rate of VTE/DVT in Asian patients particularly suffering from stroke is limited. Epidemiological studies are warranted in this regard. Based on available evidence the risk of VTE is limited in Asian population. The true replica of management guidelines initially designed for western population may not be suitable for Asians where the risk is low and most of the health expenses are managed through out-of-pocket expenditure. Scales for the assessment of VTE Risk in Patients with Acute Stroke should be designed to identify patients with high probability of developing VTE/DVT. Risk vs benefit assessment may be helpful in deciding the type of thromboprophylaxis. Non-pharmacological interventions like early mobility, physiotherapy, proper hydration, intermittent pneumatic compression may be reasonable preventive strategies for stroke patients instead of advising expensive antithrombotic medications which bear a risk of haemorrhage related complications for a non-significant reduction in mortality rates.

The authors recommend mechanical thromboprophylaxis as the first line treatment option against VTE in acute stroke patients based on its efficacy, cost effectiveness, without any additional risk of haemorrhage. Other types of prophylaxis strategies alone or in combination may be considered in specific patients after proper assessment of bleeding vs VTE risk assessment based on a validated risk stratification scale.

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#### Author's Contribution

MS and AMA conceived the idea, helped in the literature search and collected the data, and drafted the manuscript. MAA, KSA, MW, OA, MMA, and AL contributed in the literature search and data collection and write-up of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### Conflict of Interest

Authors declared no conflict of interest

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None

#### Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.