Prevention and follow-up in thromboembolic ischemic stroke: do we need to think out of the box?

Albe C. Swanepoel [1], Etheresia Pretorius [1]

[1] Department of Physiology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa

*** Corresponding Authors**

CORRESPONDING AUTHORS

Albe C Swanepoel

Department of Physiology, Faculty of Health Sciences, University of Pretoria

Private Bag x323, ARCADIA, 0007

SOUTH AFRICA

Albe.swanepoel@up.ac.za

Etheresia Pretorius

Department of Physiology, Faculty of Health Sciences, University of Pretoria

Private Bag x323, ARCADIA, 0007

SOUTH AFRICA

resia.pretorius@up.ac.za

Tel: (+27)12 420 2864

ABSTRACT

Stroke is one of the most debilitating thrombotic diseases, and world-wide it is estimated that by, 2030 23 million people will be affected. Except for the impact on the individual families, the world economy is also affected adversely. Although the medical treatment and knowledge of stroke are both increasing and well-researched, we still do not see a light in the tunnel. Currently various diagnostic tests are employed to determine the specific type of ischemic stroke as classified by the TOAST criteria. However, these tests are done after the stroke has occurred and therefore only contribute to the unquestionably crucial aspect of treating that particular stroke patient, but it does not improve prevention of future events. Prevention strategies regarding first-time stroke need urgent attention given the alarming present and future incidence of stroke. Therefore, here we discuss the importance of stroke prevention and suggest a more inclusive, perhaps “new” comprehensive approach for pre-stroke screening. Ultrastructural tests, particularly scanning electron microscopy, provide an innovative and novel advance in preventative and individualized patient-centered

precision medicine. This precise technique when used in combination with well-established methods, as well as viscoelastic methods like thromboelastography (TEG), as a screening tool to prevent stroke can ultimately alleviate the financial and economical burden of stroke and also improve quality of life. Although we appreciate the fact that this suggestion might be difficult to accept by clinicians, a bold new approach is needed to address this pandemic we call stroke.

KEYWORDS: Thromboembolic ischemic stroke; scanning electron microscopy, comprehensive approach

Introduction

Stroke, one of the most debilitating conditions, mainly results from ischemia due to occlusion or stenosis of the blood vessel (approximately 87% of stroke cases) while a few cases are attributed to haemorrhage where a blood vessel ruptures or leaks[1, 2]. Annually 17 million people worldwide are affect by stroke and in 2010 alone there were 33 million stroke survivors with many cases associated with disability [3]. About 800 000 of these cases occur in the USA [4], with primary stroke being the major contributor (around 600 000 cases) [5]. In the United States alone every 40 seconds someone suffers a stroke, while, on average, a person dies of a stroke every 4 minutes [4]. Furthermore, it is envisaged that by 2030 an additional 3.4 million people will suffer a stroke compared to 2012 [6]. A global estimate for 2030 is 23 million people suffering a primary stroke with almost 7.8 million deaths as result of stroke [7, 8].

A subsequent increase in stroke survivors (an estimated 15.2 million individuals), ascribed to the increase in the aging population, accompanied by increased strain on health- and social-care structures, is thus inevitable [6]. Although there are so many stroke survivors, survival is a double-edged sword, as it is also considered to be the foremost cause of chronic disability [5]. Almost a third of stroke survivors are permanently disabled and one fifth require institutional care after 3 months [9]. Almost half of stroke cases in the elderly result in cognitive deficits while a third affect the independence of these individuals to perform daily activities [10]. Post-stroke quality of life is therefore (mostly) synonymous with functional impairment.

500 people per 100 000 are currently living with post-stroke consequences [11] and it is suggested that by 2030, stroke-related disability will rank as the fourth leading cause of disability-adjusted life years, relating to the years lost due to illness [12]. It not only alters the

lives of those who suffered the stroke, and who most likely are disabled by it, it also influences the lives of the victim's family and loved ones as well as caregivers [13].

The financial implications are currently believed to have the following global impact:

- Stroke consumes roughly 2-4% of total global health-care expenditure [11].
- Estimations for 2030 suggest that direct medical stroke-related expenses will be triple the current value and is estimated to be $184.13 billion.
- Annual cost as a result of lost productivity, will most probably increase with 68%, to approximately $56.54 billion [6].
- The total annual cost in billion € 2010 of stroke in Europe is about 64.1 [14].
- In the USA it is the section of the working population with the most employment experience (age 45-64 years) that are expected to be hit the hardest with increased stroke incidence of 5.1% by 2030 [6].

In the current paper we discuss the importance of stroke prevention and suggest a more inclusive, perhaps "new" comprehensive approach for pre-stroke screening. **Figure 1** supplies the summary of this paper.

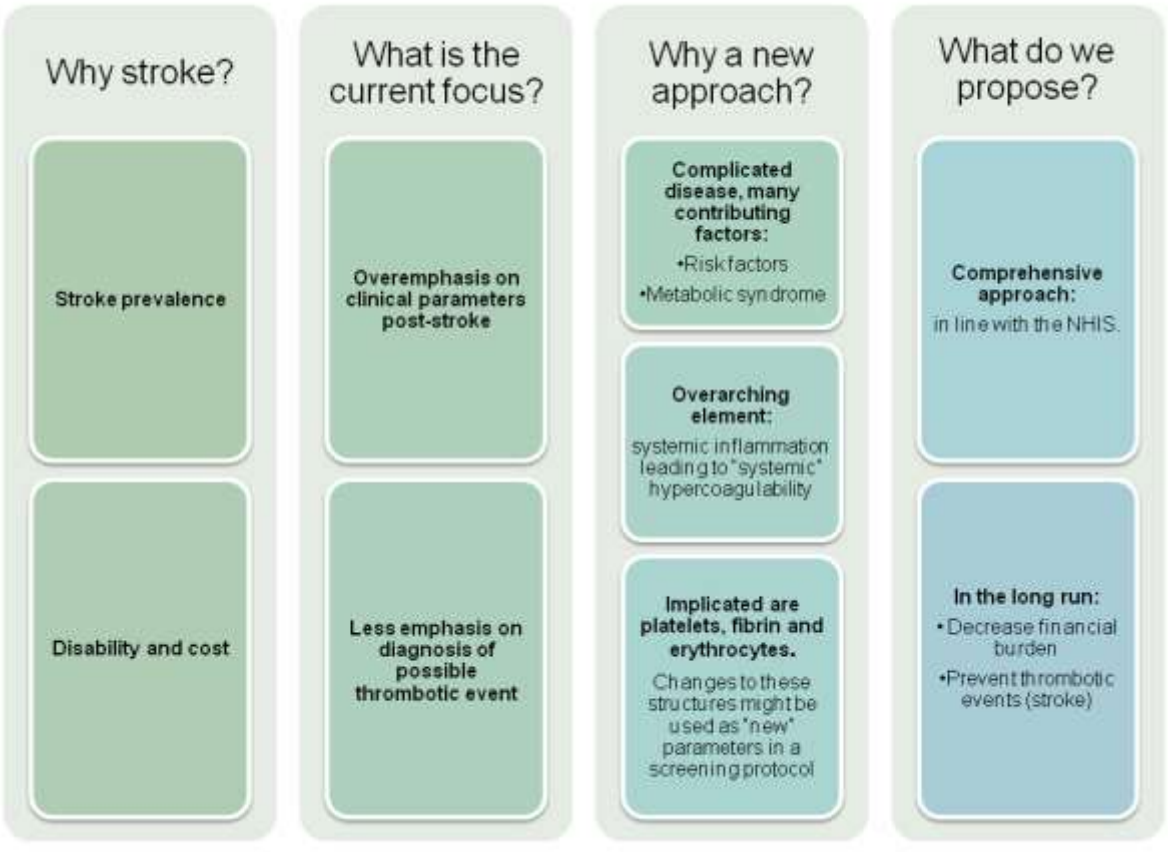

Figure 1. Synopsis of the prevention of stroke and a new comprehensive approach for pre-stroke screening.

From the above-mentioned, the indirect cost of stroke, particularly premature mortality along with lost productivity, is therefore much greater than the sum of all direct costs of stroke [15]. Unfortunately these staggering numbers only reflect the economical burden of stroke, while the costs borne by patients and their family, as well as the cost of comorbidity is not even cited [16]. Since primary stroke represents almost 80% of all stroke events, the main focus should therefore be on more effective prevention strategies to bridle the future escalation in stroke incidence and resulting disability [10, 17]

Current approach: Diagnostic testing and preventative strategies

Currently various diagnostic tests are employed to determine the specific type of ischemic stroke as classified by the TOAST criteria [18-22]. These tests are, however, after the stroke and only contribute to the unquestionably crucial aspect of treating that particular stroke patient, but it does not improve prevention of future events. Prevention strategies regarding first-time stroke need urgent attention given the alarming present and future incidence of stroke. Figure 2 shows a comparison of current diagnostic and preventative measures.

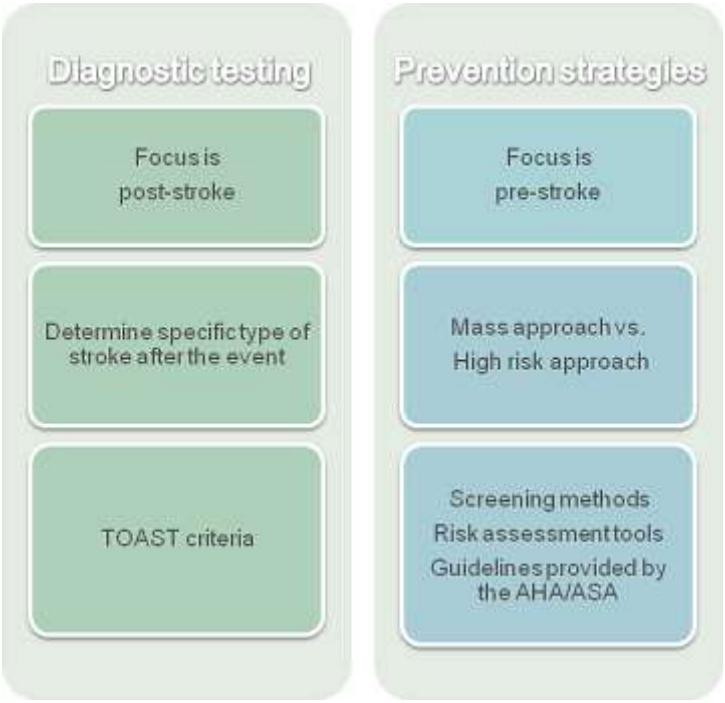

Figure 2. Comparison of diagnostic testing and preventative strategies.

With regards to prevention strategies, two core approaches are currently followed namely the ‘mass’ approach and then the ‘high risk’ approach. The first focuses on decreasing the risk factor exposure of a population while the latter concentrate on identification of specific

individuals at risk of stroke and subsequent modification or treatment of their particular risk profile [17]. Although the NIH has recently started focusing on the 'high risk' approach of individualized patient-centered precision medicine [23], the 'mass' approach specifically the two population-based intervention strategies of reducing salt intake and controlling tobacco, has had a positive effect on chronic disease prevention [24].

Different screening methods have been established over the past few years including community stroke screening [25] and ECG iPhone technology to screen for specifically atrial fibrillation, a major risk factor for stroke [26]. Risk assessment tools (including QStroke [27], FSRS [28] and the Stroke Riskometer App^{TM} [17]) are useful in the identification of individuals in need of therapeutic intervention or who may not be treated due to the presence of only 1 risk factor. It is also a practical tool to alert clinicians as well as patients of possible risk [29]. Although these tools can be used to predict stroke, they revolve around the input of risk factors and thus excludes other types of testing (specifically blood biomarkers) and subsequently individuals who are at risk of suffering a stroke due to other factors like coagulopathies, which do not form part of the traditional risk factors, will potentially fall through the cracks. Although prevention strategies utilizing a risk assessment tool are beneficial to individuals with primarily high-risk profiles, it is the group of people with mildly increased risk that show the highest number of stroke incidence [30, 31].

In 2014 Meschia and coworkers published a very useful collection of guidelines pertaining to the primary prevention of stroke [29]. This statement served as an update of the report done by Sacco and coworkers in 2006 [32]. Both these reports provide comprehensive and evidence-based recommendations for the prevention of first time stroke and transient ischemic attack. Table 1 provides a summary of the risk factors identified in 2014 [29] where screening is suggested.

Table 1: Recommendations with regards to screening protocols for specific risk factors.

Risk factor	Recommendation regarding screening
Genetic Factors	Family history may identify individuals at risk but genetic screening of general public for prevention of a first stroke not recommended
Hypertension	Regular BP screening and the appropriate treatment of patients with hypertension are recommended. Annual screening for high BP and health-promoting lifestyle modification are recommended for patients with pre-hypertension.
Atrial fibrillation (AF)	Active screening for AF in patients >65 years of age can be useful
Sickle cell anemia disease (SCD)	Transcranial doppler ultrasonography screening for children with SCD starting at 2 years of age and continuing annually to 16 years of age
HYPERCOAGULABILITY*	Genetic screening for detection of inherited hypercoagulable states or patients with or acquired thrombophilia, as possible risk factor is not well established

Thrombosis plays a critical role in the pathophysiology of stroke. Ischemic stroke has two main aetiologies: firstly carotid atherosclerotic plaque rupture and superimposed thrombus formation (contributing to about 70-80% of cases) and secondly systemic embolism of a cardiac thrombus (contributing to about 30% of cases, most common in AF patients)[33].

Atherosclerosis can be either an extended process of slow luminal narrowing (which is the "classic" concept) of a rapid process that leads to luminal obstruction (which involves plaque hemorrhage with luminal thrombosis, healing of the plaque and incorporation of the thrombus into the coronary plaque, therefore lumen narrowing and increased plaque burden).

It is troubling to note that a specific protocol of screening for hypercoagulability or necessity thereof is not established. Especially since a significant number of ischemic stroke events in younger individuals, whom exhibit none of the common arteriosclerotic risk factors, are triggered by coagulopathies (either genetic or acquired) or other coagulation defects of undetermined etiology [34]. It is clear that clinical research mainly focuses on post-stroke resulting in an overemphasis on clinical parameters after the event and less emphasis on diagnosis of a possible thrombotic event.

A new approach: a comprehensive methodology for pre-stroke screening

We therefore propose a comprehensive approach that will, in the long run, decrease the financial burden and prevent thrombotic event (stroke). This approach is needed because stroke is a complicated disease with many factors contributing to the development of stroke, including metabolic syndrome and both acquired and non-acquired risk factors.

Hypercoagulability, inflammation and infection are some of the potentially modifiable risk factors that are less well-documented [13]. Chronic inflammatory disease is associated with increased stroke risk and measurement of some inflammatory markers like hs-CRP or lipoprotein-associated phospholipase A2 in patients without cardiovascular disease may be useful in identifying individuals at risk of stroke [29]. The overarching element is therefore systemic inflammation leading to "systemic" hypercoagulability and central to this is the involvement of hyper-activated platelets, hypercoagulable fibrin and eryptotic and necrotic erythrocytes. Another well-established factor is the involvement or increased iron levels in inflammation.

The relation between iron, inflammation and hypercoagulability is well established [35-38] specifically the effect of iron on blood coagulation [39-50]. Changes to these structures might be used as "new" parameters in a screening protocol.

This novel screening protocol will have a comprehensive methodology with an individualized patient-centered precision medicine approach [23]. Precision medicine takes individual variability into account when treatment and preventative measures are considered for a patient [23]. The proposed outline for this approach model is shown in Figure 3.

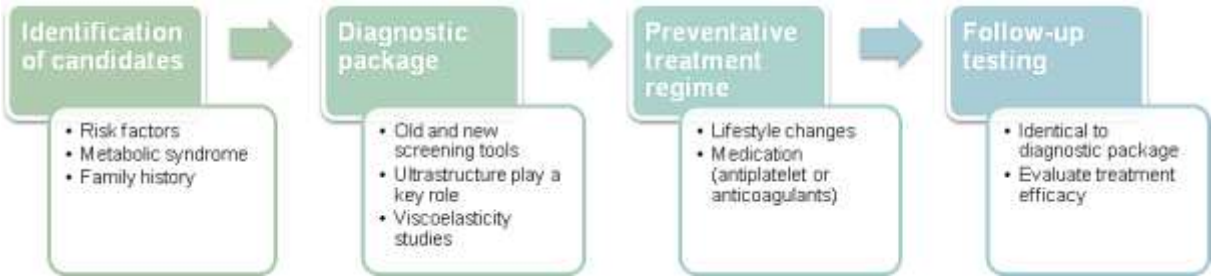

Figure 3. An outline of the suggested method for a screening protocol that incorporates old and new methods such as ultrastructural and viscoelasticity studies to prevent stroke.

A typical process will have four steps. The first step will be identification of candidates through a questionnaire or as recommended by a clinician. Included will be individuals with a family history, with the typical risk factors of stroke or that suffer from metabolic syndrome and/or other diseases that are associated with chronic inflammation.

Secondly a diagnostic package, which includes old and new screening tools, will be used to identify the person's risk of stroke. Here we suggest that ultrastructural tests, specifically scanning electron microscopy (SEM), together with traditional methods may possibly be the answer to preventative and individualized patient-centered precision medicine approach [23]. SEM is a very precise method and complements other methods like thromboelastography (TEG). Rosenson's team has established the importance of measuring blood rheology and viscosity [51, 52]. SEM has been used extensively to establish the exact morphological characteristics of platelets, fibrin networks and erythrocytes from healthy individuals as well as individuals who suffered a TEI stroke [53-58]. **Figure 4** shows the typical platelet (A), fibrin network (B) and erythrocyte morphology (C) of a healthy individual and **figure 5** shows the typical platelet, fibrin network and erythrocyte morphology of a person who suffered a TEI stroke.

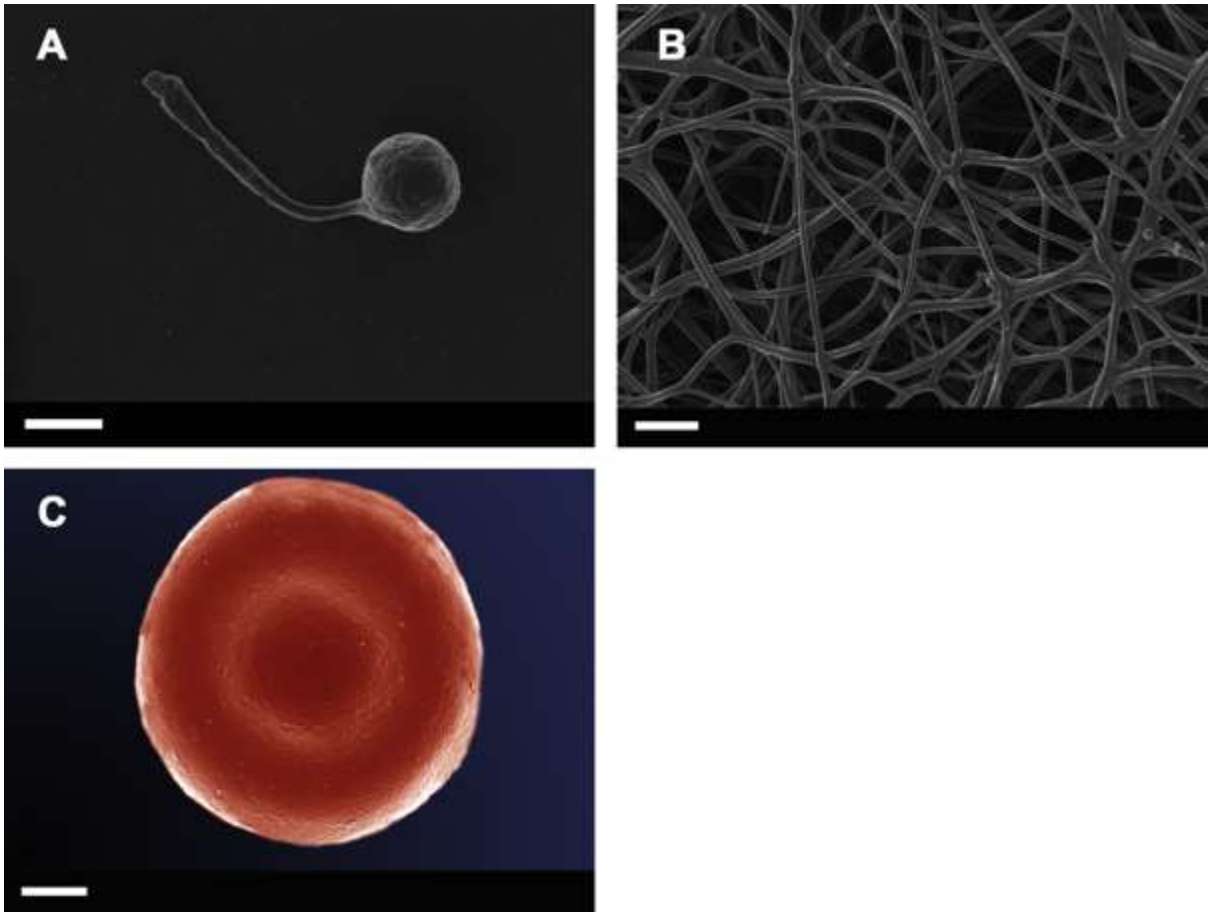

Figure 4. Healthy platelet **(A)**, fibrin network (created by adding thrombin to plasma) **(B)** and erythrocyte **(C)**. Erythrocytes have smooth membranes and are typically discoid in shape. Scale: 1μm.

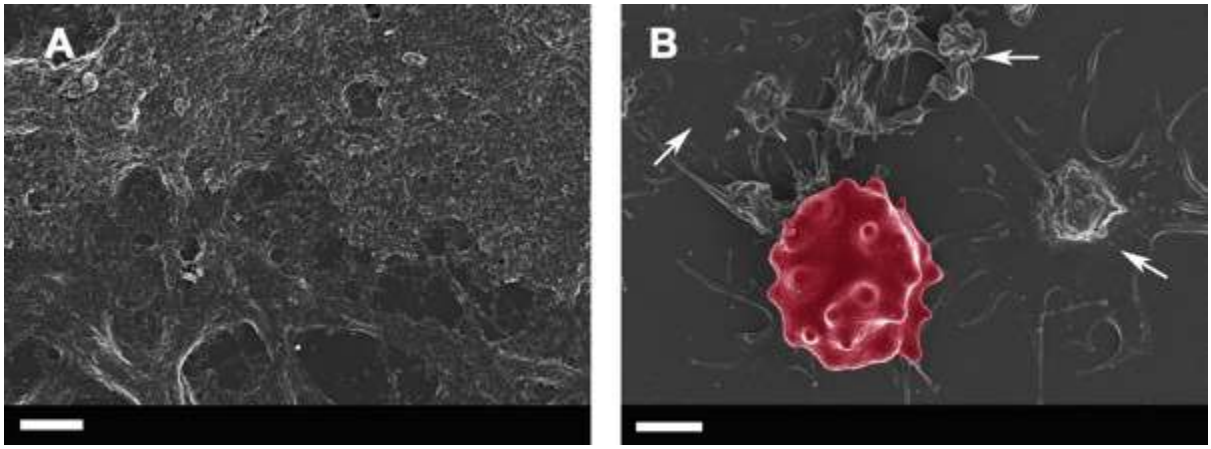

Figure 5. Typical matted, hypercoagulable fibrin fiber mat in thromboembolic ischemic stroke **(A)** and structurally changed erythrocyte with hyperactivated platelets as seen in a typical whole blood smear **(B).** Arrows show spreaded, hyper-activated platelets in close contact with an eryptotic erythrocyte. Scale: 1μm.

Since platelets play such a crucial role in the early stages of thrombus formation they form an integral part of morphological studies associated with stroke [59]. Platelets are also closely involved in atherosclerotic inflammatory response, thrombotic vascular occlusion,

formation of micro-embolisms and vasoconstriction along with plaque progression. If platelet activation persists it can have dire consequences for patients with acute coronary syndrome (ACS) increasing their risk for ischemic events and subacute stent thrombosis [60].

SEM and TEM analysis of platelet morphology have been deemed essential systemic tools in understanding neurodegenerative and other disease pathogenesis [61, 62]. Platelets from TEI stroke patients are swollen and their taut membranes are characteristic of necrosis [54]. When fibrin networks are prepared thick dense matted deposits (DMDs) are formed [57]. This altered morphology is suggested to be present long before the actual thrombotic event [63]. Erythrocytes from TEI stroke patients show elongated membrane extensions that directly interacted with DMDs of fibrin fibers. Since other thrombotic diseases like diabetes [40] that precede stroke are also associated with this specific type of interaction between erythrocytes and fibrin it suggests that this interaction is the trigger rather than the consequence of the stroke [55]. The diagnostic package will thus indicate whether an individual has a healthy clotting profile or need preventative treatment.

If an individual is deemed at risk of stroke according to their clotting profile, the third step will be a preventative treatment regime. This will include for example lifestyle changes and medication that reduce BP and LDL-C, target HDL [64] and antiplatelet agents, which have been shown to prevent stroke [29, 32, 65]. Antithrombotic therapy is the cornerstone of stroke treatment and prevention, therefore the CHADS2 score can be used to determine the specific type of antiplatelet or antithrombotic treatment do be used for each individual [33]. The treatment regime will be tailor-made for each individual, depending on the results from the diagnostic package.

Lastly the patient will undergo follow-up testing with the same techniques as used in the diagnostic package. This is in line with a comprehensive approach as well as an individualized patient-centered precision medicine approach as suggested by the NIH [23]. In the long run this preventative approach will alleviate the financial burden associated with stroke, since the cost of hospitalisation and medical care post-stroke will be eliminated if stroke is prevented. Preventing stroke will also decrease the economic burden of stroke by early detection thereby preserving the health of the working class, especially the age group 45-64 years which are foreseen to suffer the greatest number of strokes. Quality of life does not bear a price tag; stroke prevention will not only decrease mortality but also decrease chronic disability synonym with post-stroke.

Conclusion

It is reasonable to implement preventative health service programs to aid in the methodical identification and treatment of risk factors in every person demonstrating a risk at stroke [29]. Preventative strategies are essential for decreasing stroke incidence, especially with the increasing incidence of metabolic syndrome and its associated complications [66]. I quote Geoffrey Rose: “Why is so large a part of our research devoted to the “mechanics of dying”, and so little to the scientific, social and economic basis of prevention? [67]”

We already postulated in 2011 that scanning electron microscopy should be used as a screening regime in the identification of possible stroke as well as monitoring progress of stroke patients during and after treatment [57]. Ultrastructural tests, particularly scanning electron microscopy, provide an innovative and novel advance in preventative and individualized patient-centered precision medicine. This precise technique when used in combination with well-established methods as well as new methods like TEG, as a screening tool to prevent stroke can ultimately alleviate the financial and economical burden of TEI stroke and also improve quality of life. Although we appreciate the fact that this suggestion might be difficult to accept by clinicians, a bold new approach is needed to address this pandemic we call stroke.

Ethical considerations

Ethical clearance was obtained from the University of Pretoria Human Ethics Committee for the use of blood from thrombo-embolic ischemic stroke patients and healthy volunteers. All participants filled in informed consent forms.

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Conflict of Interest statement

There are no conflicts of interest to declare by any of the authors.

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