The prevalence of atrial fibrillation in patients with ischaemic stroke in a district hospital in the Western Cape

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Abbreviations

AF	Atrial fibrillation
CI	Confidence interval
CT	Computed tomography
CVA	Cerebrovascular accidents
CHC	Community health centres
DALYs	Disability adjusted life years
DOACs	Direct oral anticoagulants
EC	Emergency Centre
ECG	Electrocardiogram
ECM	Enterprise content management (electronic medical records)
GSH	Groote Schuur Hospital
HECTIS	Hospital and Emergency Centre tracking information system
HIC	High-Income Country
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Disease, Tenth Revision
INR	International normalised ratio
IQR	Interquartile range
LMIC	Low- and Middle-Income Country
MPH	Mitchells Plain Hospital
MRI	Magnetic resonance imaging
NOACs	Novel oral anticoagulants
PACS	Picture archiving and communication system
SD	Standard deviation
SSA	Sub-Saharan Africa

TIA	Transient ischaemic attack
UCT	University of Cape Town
WHO	World Health Organization
YLD	Years lived with disability

PART A: LITERATURE REVIEW

Objectives of literature review

- To gain an understanding of the prevalence of atrial fibrillation in patients with ischaemic stroke in high-, as well as low- and middle-income countries.
- To understand the aetiology of ischaemic stroke and atrial fibrillation.
- To evaluate the prevalence of atrial fibrillation in the general population.
- To understand and compare the morbidity and mortality of cerebrovascular accidents with and without atrial fibrillation
- To assess current screening practices for atrial fibrillation and to understand the challenges experienced
- To briefly explore the burden of disease that cerebrovascular accidents have on the South African population
- To gain insight into the costs incurred on the health system by cerebrovascular accidents.

Literature search strategy, including inclusion, exclusion and quality criteria

The literature search strategy consisted of a using a variety of online medical and scientific databases including PubMed, NBCI, Google Scholar, and EMBASE, to maximize yield of relevant references to this study. Searches were conducted using MeSH terms, which included "stroke"," cerebrovascular accident", "Atrial fibrillation", "ECG", "cardiac arrhythmia" "cardiovascular disease"," prevention", "low-income", "high-income", "burden of disease", "epidemiology" "prevalence", "South Africa"," Sub-Saharan Africa", "Africa", "anticoagulation", "disability adjusted life years". Searches included various combinations of terms and words mentioned above. Abstracts and titles of studies that were identified from the search results were reviewed individually. Full text articles were obtained for those that were considered relevant.

The inclusion criteria used were applicable studies published in English in peer reviewed journals and not older than 25 years. Full text articles that could not be obtained via the university library portals, or that required paid subscriptions, or needed to be purchased, were excluded. Only the English abstracts and papers were reviewed, other language-journals were excluded. Further studies for possible inclusion were identified by searching through the references of the studies already identified as relevant for inclusion in a snowballing fashion.

The MMed literature review does not require a formal assessment of the quality of papers and this was therefore not done. Articles were however screened for applicability and whether or not the results were internally and/or externally valid.

Summary of literature

Introduction

Cerebrovascular disease remains one of the leading causes of morbidity and mortality globally. It affects 15 million people annually and is responsible for 5 million deaths per annum, contributing to the growing burden of non-communicable diseases (NCDs) worldwide. (1,2) Stroke, also known as cerebrovascular accident (CVA), is defined as a neurologic deficit caused by a cerebrovascular problem which persists for more than 24 hours or causes death within 24 hours. (3) It is characterised by focal or global cerebral functional impairment, affecting both motor and sensory function, and rapidly evolving. An estimated 80% of strokes globally are ischaemic in nature, and the rest non-ischaemic, either being haemorrhagic or secondary to a different cause. International data states that one fourth of all ischaemic strokes are cardio-embolic in nature. (3,4) Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. Embolization of a mural thrombus in a patient with AF is the most common mechanism of cardio-embolic stroke, and patients with AF have a fivefold increased risk for developing a stroke. (4–6) There is a paucity of data available reporting the prevalence of AF in the urban population in South Africa, particularly in patients with CVAs. This aim of this literature review was to establish the gain an understanding of the prevalence of atrial fibrillation in patients with an ischaemic stroke and to explore challenges with regards to the screening, diagnosis and management thereof.

Aetiology

An estimated 80% of strokes globally are ischaemic in nature, and the rest non-ischaemic, either being haemorrhagic or secondary to a different cause. (4) The list is extensive and not limited to the following but the commonly seen causes include cervicocephalic arterial dissection; cavernous and sagittal sinus thrombosis; Hypercoagulable state due to deficiencies of protein S, protein C, or antithrombin and factor V Leiden mutation; antiphospholipid syndrome; sickle cell disease; myeloproliferative disorders (e.g., leukaemia, lymphoma); Vasculitis; neurosarcoidosis; neurocysticercosis; bacterial and tuberculous meningitis, as well as other infectious disease, which often occurs in immunodeficient patients predominantly HIV positive patients with opportunistic infections such toxoplasmosis or cryptococcal disease. (4,7,8)

Maredza et al., estimates that in the South African setting, 71% are ischaemic, 21% haemorrhagic and the remainder secondary to a different cause, including vasculitis, HIV associated opportunistic infections, space-occupying lesions and trauma (9,10) International data states that 25% of all ischaemic strokes are cardio-embolic in nature. (3,4) Embolization of a mural thrombus in a patient with AF is the most common mechanism, and patients with AF have a fivefold increased risk for developing a stroke (4–6) as well as a twofold increased risk of silent cerebral infarction. (5) The presence of AF in patients

with newly diagnosed strokes is associated with prolonged hospitalisation, increased persistent disability, greater severity of disease, and elevated healthcare costs. (3,11,12) In addition to this, strokes that occur in the setting of AF have an increased risk of mortality compared to strokes of other aetiologies. (5)

Prevalence

Atrial fibrillation is an abnormal cardiac rhythm characterized by rapid and irregular beating of the atria, (7) and is defined as one or more episodes of at least 30 seconds of atrial arrhythmia with no distinct P-waves. (13) AF is the most common cardiac arrhythmia worldwide, has an estimated prevalence of 0,5-3% in the general population within western countries (6,13,14), with a higher prevalence in males as compared to females. (5,14). Standard AF risk factors include an older age, male sex, smoking, obesity, hypertension, diabetes, myocardial infarction, heart failure, valvular heart disease, and cardiac surgery. (4,5) AF can lead to thrombus development within the atria, particularly the left atrial appendage, which can cause thromboembolic events. (15)

AF can be classified as: paroxysmal or intermittent AF, which involves intermittent episodes that resolve spontaneously within a week; persistent AF, which is continuous sustained for more than one week, which can be reversed through surgical or pharmacological intervention, and permanent AF, in which the arrhythmia is constant but not reversible (16), and in which the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. (16,17). Other types of AF not mentioned frequently in the literature includes long-standing persistent AF, which is AF that is continuous for more than 12 months; non-valvular AF; and “lone” AF. (4,7,17) Atrial flutter is classified as a regular supraventricular tachycardia which is also due to a re-entry circuit within the atria and is also associated with an increased risk of stroke. (4,7,16)

Current data, albeit sparse, indicates that the prevalence of AF in developing countries is slightly lower than that of the developed world. (14) Despite this lower prevalence of AF in developing countries, the number of AF related deaths increased 196% from 1990 to 2013 in Sub-Saharan Africa (SSA) (18), as did the number of deaths from strokes, particularly ischaemic strokes with a 102% increase. (18) As AF becomes more prevalent with age, the incidence of AF is estimated to increase progressively in the future with the increased mortality and morbidity associated with it. (14) Interestingly, an observational study done by Prefasi et al looked at the prevalence of atrial fibrillation in young patients (less than 50 years of age) suffering from ischaemic stroke, which showed that AF is more common than expected in patients with young stroke with increased National Institutes of Health Stroke Scale (NIHSS) scores. (19)

In the United States, AF accounts for approximately 15% of all strokes, 36% of strokes for individuals aged >80, and up to 20% of cryptogenic strokes. (12) This means that AF accounts for 100 000-125 000 embolic strokes per year, of which more than 20% are fatal. (12) A study conducted in Greenland

by Bjorn-Mortensen et al showed that more than 30% of patients diagnosed with ischaemic stroke had AF and only 5 % were diagnosed prior to stroke – this article suggests that unknown AF is a substantial risk factor for stroke (20). In a Swedish cross-sectional study over a 5 year period, a combination of data from Riks-Stroke Swedish Registry and from the Patient Register showed that 33.4% patients with ischemic stroke had existing, or newly diagnosed AF. (21) Data on the general prevalence and incidence of AF in Africa is sparse, particularly in South Africa with small studies estimating it to be 5.6 cases per 100 000 per year (22), with no data available about the prevalence of AF in patients with ischaemic strokes in an urban environment. In 2008, Bertram et al., estimated that there are 75 000 strokes in South Africa each year, with 25 000 of these fatal within the first month. (23)

Morbidity and Mortality

Cerebrovascular disease remains one of the top causes of morbidity and mortality worldwide, both in high-income countries (HICs) and low- and middle-income countries (LMICs). (4) In South Africa cerebrovascular disease was the fourth leading cause of death in 2016, responsible for 5.1% of deaths (24) , and the leading cause of death in individuals 65 years and older. (24) Globally approximately 3% of total health care system resources are dedicated to stroke, indicating that cerebrovascular accidents contribute to a significant economic burden on countries. (9,25) Stroke severity and in-hospital mortality are also significantly greater in those with AF. (16,26,27) AF occurs most commonly in older populations, therefore, the increased life expectancy in both developed and developing countries means that AF-related stroke has become a growing global public health concern. (16) The associated costs of treating the consequences of AF potentially place a significant economic burden on health systems and society. (16) A systemic review done by Andrew et al suggested that stroke prevention is difficult mainly due to the large percentage of cases of undiagnosed AF in society and poor compliance to medication for those with diagnosed AF. (16)

Diagnostics and screening

Many patients with AF experience no symptoms; between 24% and 50% of cases are reported as undiagnosed. (16,28) Asymptomatic AF is also more common in those with permanent AF than in those with paroxysmal AF. (4,12,16) Consequently, AF is often not diagnosed until patients present to hospital with a stroke, or it is incidentally diagnosed during routine electrocardiogram (ECG) examinations. (16) Alarmingly up to 25 % of patients with AF-related stroke only have this arrhythmia diagnosed at the time of the stroke. (28)

This is concerning since asymptomatic AF affords the same stroke risk as symptomatic AF, and if left undiagnosed, may provide additional risks associated with the lack of access to preventive treatments. (16) Although the risk of stroke related to AF can be reduced by 64–70% by oral anticoagulation, underutilisation of this effective treatment and delayed diagnosis remain major obstacles. (13,28)

A trial done by Strahenberg et al in Germany aimed to review the diagnosis of paroxysmal AF by early and prolonged continuous Holter monitoring in patients with cerebral ischaemia presenting in sinus rhythm. The study showed that prolongation of Holter monitoring in patients with cerebral ischaemic events increased the rate of detection of paroxysmal AF up to day 7 which would lead to a relevant change in therapy in a substantial number of patients. (13) The study recommended that prolonged Holter monitoring should be considered for all patients with unexplained cerebral ischaemia. (13) This is echoed in another two studies, the first by Andrew et al where it is stated that the diagnosis of intermittent AF may also be complicated by the fact that it may not be identified by a single ECG reading. Continuous ECG monitoring for periods of 24 hours or more in stroke patients can approximately double the number of AF cases diagnosed when compared to a single short ECG reading. (16,29) The second article, echoing the same sentiment by Go et al, the KP-RHYTHM Study, which concludes that a greater burden of AF (i.e. the amount of time spent in atrial fibrillation) identified using a non-invasive, 14-day continuous electrocardiography monitoring strategy is associated with a higher risk of ischaemic stroke and arterial thromboembolism in adults with paroxysmal AF that is independent of known stroke risk factors. (15)

This diagnostic modality may be the gold standard but for many parts of South Africa prolonged Holter monitoring for all patients with cerebral ischaemia would be difficult to achieve. Nevertheless characterizing the burden of AF in patients with paroxysmal AF could assist patients and physicians in having a more informed, shared decision-making discussion about stroke prevention strategies. (15)

A review done by Yang et al showed that single timepoint pulse palpation, when patients present for routine visits, together with confirmatory ECG in elderly adults is potentially feasible and beneficial for primary stroke prevention. additional screening with twice-daily intermittent ECGs for 2 weeks may be warranted in patients older than 75 years. (30)

In a Canadian study by Tarride et al, screening for AF in seniors greater than 65 years of age during routine appointments with family physicians was a cost-effective strategy compared with no screening, and that single lead-ECG is a highly cost effective strategy with an incremental cost per quality-adjusted life-year (QALY) gained of CAD$4788. (31) Current European Society of Cardiology guidelines recommend opportunistic screening for AF by pulse taking or ECG rhythm strip instead of a systematic approach in people more than 65 years of age. (28,32) AF satisfies most of the World Health Organization (WHO) criteria for a disease suitable for screening. (28) Despite this and the studies mentioned above the U.S. Preventive Services Task Force (USPSTF), backed by the American Heart Association (AHA), in recent months stated that there is not enough evidence to support ECG screening for AF in asymptomatic adults ages 65 and older. (33)

Nonetheless, newer inexpensive technologies, including handheld devices, are promising tools for screening. (30) Tools such as smart phone-based devices have made AF screening in the community

more feasible. However the sensitivities and positive predictive values of the current versions of these automated diagnostic algorithms for AF have to be further interrogated to increase the cost efficiency of such screening programmes. (28) Karmen et al performed a study on the clinical value of using an Apple Watch to monitor heart rate and the study concluded that wearable devices may be helpful in cardiac monitoring and detecting AF but more studies are needed on this topic. (34)

Ander et al published a recent study where they demonstrated that patients with cryptogenic stokes who have moderate to severe left atrial enlargement (LAE) on transoesophageal echocardiography were more likely to have AF than non-AF, and that the likelihood increases with age and severity of LAE, and that anticoagulation should be considered in cryptogenic stroke patients with severe LAE , especially those patients who require insertable cardiac monitors. (35)

Treatment

A study done in South Africa aimed to review the treatment modalities of AF on a broad scale. Most reputable studies focus on treatment modalities in the developed world. Jardine et al attempted to merge this gap and assess the treatment modalities of AF in the South African population. The study showed that the most prevalent clinical characteristic was hypertension. (65.9%) Rhythm control was used in 36.1% of patients with class IC and class III antiarrhythmic agents, mainly Amiodarone, while rate control, mainly with beta-blockers, was used in the remainder of the patients. Concomitant use of other cardiovascular drugs was high, and 75.2% of patients were on warfarin for stroke prevention. Therapeutic success, as defined by either the presence of sinus rhythm or rate-controlled AF, was achieved in 86.8% of patients as judged clinically by the treating physician, but in only 70.2% according to the ECG criterion of a heart rate less than or equal to 80 beats per minute (bpm) at rest, using the 'lenient' rate control criterion of ≤110 bpm proposed by the RACE II trial 90.6% of patients would have fulfilled this definition. (36) Anticoagulation plays a major role in the treatment of AF worldwide. (13,37,38) Medicare registries and clinical trials have demonstrated the protective effect of Vitamin K antagonists such as warfarin on reducing stroke events. (13,37) Furthermore, subtherapeutic anticoagulation results in 5-times the odds of an ischemic stroke. (37,39)

Risk stratification is particularly useful in deciding when to initiate treatment in patients with Non-Valvular AF. Several scoring systems have been developed to better manage patients with Non-Valvular AF. The two most popular stratification tools are the CHA_2DS_2-VASc and $CHADS_2$ scores, CHA_2DS_2-VASc being the updated scoring system of the original $CHADS_2$ score. (3,21,37) These tools incorporate the major risk factors for ischaemic stroke and give an unadjusted ischaemic stroke rate as a percentage per year. The components include congestive heart failure, hypertension, age equal to or greater than 75, diabetes, prior stroke or transient ischaemic attack, vascular disease, and female sex. (37) Generally speaking a score of ≥2 is high risk for thromboembolism and is a strong indication

for anticoagulation therapy. Patients who qualify for and are initiated on oral anticoagulation have an increased risk of bleeding (3,37,39,40). To obtain a bleeding risk the HAS-BLED scoring system was developed. The HAS-BLED score is a simple scoring tool that is used to determine a patient's annual bleeding risk. Oral anticoagulation bleeding risk outweighs the benefits of treatment if the HAS-BLED score exceeds the $CHADS_2$ score in patients with a $CHADS_2$ score of >2. (37) The components of the HAS-BLED score are hypertension, abnormal renal or liver function, stroke, bleeding history, labile International normalised ratio (INR), elderly and drug or alcohol abuse. (37)

A fairly recent South African study by Ntlokotsi et al essentially looked at patients with valve replacements, with or without AF, over a three-year period with the optimum INR target ranges for all participants estimated to be 2.0– 3.5. (37,41) This study focused on South African black patients, but from the relevant data and references in the study the authors conclude that optimum Caucasian-based INR are the same for black patients. Alarming though the quality of warfarin anticoagulation of the participants with valve replacement was found to be inadequate as indicated by percentage time in treatment range (TTR) which was 49.7% for all study participants compared with the ideal TTR of 70% and above. (41) With similar results demonstrated by Sonuga et al, looking at anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. (42) Patients with low-percentage TTR (a reflection of large variation in INR over time) are at a higher risk of warfarin-related major bleeding, including haemorrhagic stroke and gastrointestinal bleeding, and thromboembolic events. (40) Possible explanations for warfarin's TTR in this study include non-compliance, drug-drug interaction, drug- food interactions and patient comorbidities. (37,43)

Multiple alternatives to warfarin, have been successfully developed for AF stroke prevention. These are more commonly known as novel- or direct-acting oral anticoagulants (NOACs and DOACs), and include Factor IIa antagonist dabigatran, and Factor Xa antagonist rivaroxaban and apixaban. (44) The ROCKET-AF, ARISTOTLE and RE-LY studies have found the DOACs to be non-inferior to warfarin, and in some cases superior. (37,45–47) Dabigatran was associated with less stroke rates in non-valvular AF compared to patients on dose-adjusted warfarin, with a significantly decreased risk of life-threatening intracranial bleeds compared with warfarin. (37,47) Rivaroxaban showed similar results, with a significant reduction in fatal bleeds in comparison with warfarin (37,45), and similarly Apixaban was found to be more effective than warfarin in preventing stroke and systemic embolism with lower rates of bleeding. (37,46) The DOACs require less monitoring and have fewer drug interactions than the warfarin, but they do have distinct disadvantages. (3,37) A huge limiting factor, particularly in LMIC is the cost associated with the DOACs and Warfarin was found to be significantly more cost-effective than the DOACs, even when a wide range of warfarin-related expenses was included. (39)

Lastly the CAABL-AF (California Study of Ablation for Atrial Fibrillation) demonstrated that in this large population-based study of hospitalized patients with a diagnosis of nonvalvular AF undergoing ablation, the risk of adverse outcomes after ablation was associated with lower mortality, and lower ischaemic stroke and haemorrhagic strokes than that observed in nonablated patients. (48)

Costs

Globally, approximately 3% of total health care system resources are dedicated to stroke indicating that cerebrovascular accidents composes a significant economic burden on countries. (9,25) There is a paucity of local data that describes the financial impact of stroke care. The burden of disease due to stroke in 2008 in South Africa was 564 000 Disability adjusted life years (DALYs). Of this, 17% is contributed by Years lived with disability (YLD). (23) In Maredza et al., it is stated that the 'total direct costs of strokes were estimated to be 2.5-4.2 million in the year 2012 in a small rural community in South Africa'. (9). This analysis is based on a population of approximately 90 000 people residing in the Agincourt sub-district of Mpumalanga province, north-east of South Africa. (9) In contrast, a study done in the United States in 2008 showed that the total direct and indirect costs of stroke was estimated to cost the economy an estimated 65.5 Billion dollars, where the indirect costs incurred were due to loss of productivity resulting from morbidity and mortality. Although the patient profile and demographics of the United States are vastly different to South Africa, these studies highlight the significant disease burden that CVAs pose on the economy of countries. (25) In addition to this, informal stroke care, which is carried out by caregivers, often being relatives and comprising of community-based activities; domestic activities; and personal activities of daily living, are often overlooked, but remains of utmost importance to maintain stroke survivors in the community resulting in an additional economic and social burden. (25,49)

Conclusion

Atrial fibrillation is a major risk factor for developing ischaemic cerebrovascular accidents, as well as other cardio-embolic complications, particularly in our urban environments. To the researches knowledge there is a paucity of data available reporting on the prevalence of AF in the urban population, particularly in patients with CVAs. With the increasing population life expectancy, and other cardiovascular disease, such as hypertension, diabetes, congestive cardiac failure and valvular heart disease the prevalence of AF and its complications will surely increase. Although the risk of stroke related to AF can be reduced significantly by oral anticoagulation, underutilisation of this effective treatment and delayed diagnosis remain major obstacles. Routine screening practices to detect asymptomatic AF in LMIC's is lacking. and up to 25 % of patients with AF-related stroke only have this arrhythmia diagnosed at the time of the stroke. Atrial fibrillation is a modifiable risk factor but challenges with regards to screening, diagnosis and management hampers effective control.

Identification of gaps in the literature, or needs for further research

- There is a paucity of data that assesses the prevalence of atrial fibrillation in patients with stroke, especially in LMIC's.
- Challenges and barriers to perform effective primary screening for AF (in asymptomatic patients) should be explored.
- Challenges and barriers to perform effective secondary screening for AF (in patients with an ischaemic stroke) should also be explored.
- Barriers and challenges to effective and safe anticoagulation practices should be explored.

References

1. Wolfe CDA. The impact of stroke. British Medical Bulletin. 2000;56(2):275-286. Avaiable on website https://doi.org/10.1258/0007142001903120

2. Observatory GH. Deaths from NCDs. 2008; World Health Organization. Deaths from NCDs. Available from website http://www.who. int/gho/ncd/mortality_morbidity/ncd_total/en/, year 2008

3. Di Giosia P, Giorgini P, Ferri C. Considerations on stroke in atrial fibrillation despite anticoagulation. J Cardiovasc Med [Internet]. 2018;19(suppl 1):e54–7. Available from: http://insights.ovid.com/crossref?an=01244665-201802001-00014

4. Marx JA, Hockberger RS, Walls RM. Rosen’s Emergerncy Medicine, Concepts and Clinical Practice, 8th Edition. 2014. 1363-1374 p.

5. Magnani JW, Rienstra M, Lin H, Sinner MF, Lubitz S a, Mcmanus DD, et al. Atrial fibrillation: Current knowledge and future directions in epidemiology and genomics. Circulation. 2011;124(18):1982–93.

6. Huisman M V., Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 2017;69(7):777–85.

7. Overview of atrial fibrillation - UpToDate. Available from website https://www.uptodate.com/contents/overview-of-atrial-fibrillation/; year 2018

8. Dževdet Smajlović. Strokes in young adults : epidemiology and prevention. 2015;157–64. Published online 2015 Feb 24. doi: 10.2147/VHRM.S53203

9. Maredza M, Chola L, Economic burden of stroke in a rural South African setting, MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. 2017;26–32.

10. Bryer A, Connor MD, Haug P, Cheyip B, Staub H, Tipping B, et al. G UIDELINE South African guideline for management of ischaemic stroke and transient ischaemic attack 2010 : A guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. 2010;100(11).

11. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11(11):639–54.

12. Reiffel JA. Atrial Fibrillation and Stroke: Epidemiology. Am J Med [Internet]. 2014;127(4):e15–6.

13. Haeusler, K.G., Tütüncü, S. & Schnabel, R.B. Curr Neurol Neurosci Rep, Detection of Atrial Fibrillation in Cryptogenic Stroke. (2018) 18: 66:1-7. Available from https://doi.org/10.1007/s11910-018-0871-1

14. Fan X, Zhang S. The Optimal Treatment For Atrial Fibrillation In Less Developed Countries. JAFIB Journal of Atrial Fibrillation [Internet]. 2014;7(3). Available from: http://www.jafib.com/published/webFormat/Shu_Zhang/shu_zhang.pdf

15. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation The KP-RHYTHM Study. 2018;3(7):601–8.

16. Andrew NE, Thrift AG, Cadilhac DA. The prevalence, impact and economic implications of atrial fibrillation in stroke: What progress has been made? Neuroepidemiology. 2013;40(4):229–39.

17. Johansson C, Johansson L. Incidence , Type of atrial fibrillation and risk factors for stroke : a population-based cohort study. 2017;53–62.

18. Mensah GA, Roth GA, Sampson UK, Moran AE, Feigin VL, Forouzanfar MH, Naghavi M, Murray CJ, . Mortality from cardiovascular diseases in sub-Saharan Africa, 1990-2013: A systematic analysis of data from the Global Burden of Disease Study 2013 [Internet]. Vol. 26, Cardiovascular Journal of Africa. 2015. p. S6–10. A

19. Prefasi D, Martínez-Sánchez P, Rodríguez-Sanz A, Fuentes B, Filgueiras-Rama D, Ruiz-Ares G, et al. Atrial fibrillation in young stroke patients: Do we underestimate its prevalence? Eur J Neurol. 2013;20(10):1367–74.

20. Bjorn-Mortensen K, Lynggaard F, Pedersen ML. High prevalence of atrial fibrillation among Greenlanders with ischemic stroke - Atrial fibrillation found in more than 30% of cases. Int J Circumpolar Health. 2013;72(1):2–4.

21. Friberg L, Rosenqvist M, Lindgren A, Terént A, Norrving B, Asplund K. High Prevalence of Atrial Fibrillation Among Patients With Ischemic Stroke. Stroke [Internet]. 2014;45(9):2599–605. Available from: http://stroke.ahajournals.org/lookup/doi/10.1161/STROKEAHA.114.006070

22. Stambler BS, Ngunga LM. Atrial fibrillation in sub-saharan Africa: Epidemiology, unmet needs, and treatment options. Int J Gen Med. 2015;8:231–42.

23. Bertram MY, Katzenellenbogen J, Vos T, Bradshaw D, Hofman KJ. The disability adjusted life years due to stroke in South Africa in 2008. Int J Stroke. 2013;8(100 A):76–80.

24. StatsSA. Mortality and Causes of Death in South Africa , 2006 : Findings from Death Notification. Mortality [Internet]. 2008;(June):1–74. Available from: http://www.statssa.gov.za/Publications/P03093/P030932006.pdf

25. Antonio Di Carlo, Human and economic burden of stroke, Age and Ageing, 2009;(January)38(1):4–5. Available from: https://doi.org/10.1093/ageing/afn282

26. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet [Internet]. 2016;388(10050):1161–9. Available from: http://dx.doi.org/10.1016/S0140-6736(16)30968-0

27. Huey-Juan L, A. WP, Margaret , et al. Stroke Severity in Atrial Fibrillation. Stroke [Internet]. 1996 Oct 1;27(10):1760–4. Available from: https://doi.org/10.1161/01.STR.27.10.1760

28. Chan N-Y. Systematic Screening for Atrial Fibrillation in the Community: Evidence and Obstacles. Arrhythmia Electrophysiol Rev [Internet]. 2018 Mar;7(1):39–42. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29636971

29. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of Ambulatory 7-Day ECG Monitoring for the Detection of Atrial Fibrillation and Flutter After Acute Stroke and Transient Ischemic Attack, Stroke. 2004;35:1647–1651

30. Yang D. Should patients undergo atrial fibrillation screening for primary stroke prevention ?; Clinical Correlations; 26 July 2018; Available from website https://www.clinicalcorrelations.org/2018/07/26/should-patients-undergo-atrial-fibrillation-screening-for-primary-stroke-prevention/

31. Tarride J, Quinn FR, Blackhouse G, Sandhu RK, Burke N, Gladstone DJ, et al. Training / Practice Health Policy and Promotion Is Screening for Atrial Fibrillation in Canadian Family Practices Cost-Effective in Patients 65 Years and Older ? Can J Cardiol [Internet]. 2018;34(11):1522–5. Available from: https://doi.org/10.1016/j.cjca.2018.05.016

32. Fitzmaurice DA, Hobbs FDR, Jowett S, Mant J, Murray ET, Holder R, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. BMJ [Internet]. 2007/08/02. 2007 Aug 25;335(7616):383. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17673732

33. Lou NA 2018. USPSTF : Insufficient Evidence for Routine Afib Screening- Final statement cites unclear benefit of treating asymptomatic ECG-detected Afib, MedPage Today.

Available from website: https://www.medpagetoday.com/cardiology/arrhythmias/74437; 7 August 2018

34. Karmen CL, Reisfeld MA, McIntyre MK, Timmermans R, Frishman W. The Clinical Value of Heart Rate Monitoring Using an Apple Watch. Cardiol Rev [Internet]. 9000;Publish Ahead of Print. Available from: https://journals.lww.com/cardiologyinreview/Fulltext/publishahead/The_Clinical_Value_of_Heart_Rate_Monitoring_Using.99708.aspx

35. Ander T, Mcpheeters C, Miller L, Wise E, Liu R, Shah J, et al. Cryptogenic Ischemic Stroke Patients with Left Atrial Enlargement are More Likely to Have Paroxysmal Atrial Fibrillation (P6.243). Neurology [Internet]. 2018 Apr 10;90(15 Supplement):P6.243. Available from: http://n.neurology.org/content/90/15_Supplement/P6.243.abstract

36. Jardine RM, Fine J, Obel IW. A survey on the treatment of atrial fibrillation in South Africa [Internet]. Vol. 104, South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde. 2014. p. 623–7.

37. Laäs DJ, Chb MB, Naidoo M, Chb MB, Medicine S, SAMJ. Oral anticoagulants and atrial fibrillation : A South African perspective. 2018;108(8):640–6.

38. Jardine RM, Sa FCP, Fine J, Neurology FCPSA, Musicology B, Obel IWP. A survey on the treatment of atrial fibrillation in South Africa Clinical characteristics. 2013; pg 623-627

39. Laäs DJ, Chb MB, Naidoo M, Chb MB, Medicine S, SAMJ. An evaluation of warfarin use at an urban district-level hospital in KwaZulu-Natal Province , South Africa. 2018;108(12):1046–50.

40. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden : reports of time in therapeutic range , major bleeding , and thrombo-embolic complications from the national quality registry AuriculA . 2011;32(18).

41. Ntlokotsi S, Moshesh MF, Mntla P, Towobola OA, Mogale MA. Optimum INR intensity and therapeutic INR control in patients with mechanical heart valve prosthesis on warfarin oral anticoagulation at Dr George Mukhari academic hospital : a three-year retrospective study Optimum INR intensity and therapeutic INR control in patients with mechanical heart valve prosthesis on warfarin oral anticoagulation at Dr George Mukhari academic hospital : a three-year retrospective study. Journal of South African Family Practice, Vol 60, No 6 (2018); pg 192-196.

42. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. African J Prim Heal care Fam Med. 2016;8(1):e1–8.

43. Lopes D, Ph D, Hylek EM, Hanna M, Al-khalidi HR. Apixaban versus Warfarin in Patients with Atrial Fibrillation., N Engl J Med 2011; 365:981-992, September 15, 2011

44. Neal MJ. Medical Pharmacology at a Glance. 6th ed. Chichester, West Sussex: Wiley-Blackwell, 2009:44-45.

45. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med [Internet]. 2011 Aug 10;365(10):883–91.

46. Granger CB, Alexander JH, McMurray JJ V, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med [Internet]. 2011 Aug 27;365(11):981–92.

47. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med [Internet]. 2009 Sep 17;361(12):1139–51. Available from: https://doi.org/10.1056/NEJMoa0905561

48. N. SU, Beate D, A. AE, Nayereh P, Yingbo Y, Eric N, et al. CAABL-AF (California Study of Ablation for Atrial Fibrillation). Circ Arrhythmia Electrophysiol [Internet]. 2018 Jun 1;11(6):e005739. Available from: https://doi.org/10.1161/CIRCEP.117.005739

49. H.M. Dewey, A.G. Thrift, C. Mihalopoulos , R. Carter, R.A.L. Macdonell, J.J. McNeil, and G.A. Donnan, . Informal Care for Stroke Survivors. Stroke [Internet]. 2002 Apr 1;33(4):1028–33.

PART B: MANUSCRIPT IN ARTICLE FORMAT

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Abstract

Background

Cerebrovascular disease remains one of the leading causes of morbidity and mortality globally. In South Africa, cerebrovascular disease was the fourth leading cause of death in 2016, responsible for 5.1 % of all deaths - the leading cause of death in individuals 65 years and older. Atrial fibrillation accounts for 15% of all strokes and a 25% of patients with AF-related stroke have this arrhythmia diagnosed at the time of the stroke.

Objectives

This study sets out to determine the prevalence of atrial fibrillation in patients with ischaemic stroke, as confirmed on CT scan, at a district level hospital in the Western Cape, South Africa.

Methods

This descriptive study was conducted at Mitchell's Plain Hospital in Cape Town and data was collected over a year. Patients diagnosed with a stroke were identified from an electronic patient register and relevant radiology and clinical data was sourced retrospectively. The diagnosis of ischaemic stroke was confirmed by a CT scan report and ECGs were independently screened by two Emergency Physicians. Categorical data was described in percentages and descriptive statistics. Continuous variables were described by median and interquartile range (IQR). Statistical significance is defined as a $p<0.05$. Categorical data was compared using the Fisher's exact test. This project has been approved by UCT Human Research Ethics Committee [790/2018].

Results

The proportion of adult patients with a diagnosis of stroke was 2%. Of those, 64% had ischaemic strokes, 9% had intracranial bleeds, 20% did not have a CT scan and 7% had stroke mimics. 11% of all participants with ischaemic stroke had atrial fibrillation, 67% of those presumed new. A total of 90 (22%) of all participants with ischaemic stroke was less than 51 years of age. The mortality rate was statistically higher in patients who had AF.

Conclusion

The results from this study suggests that screening practices to detect both Atrial Fibrillation in asymptomatic patients, as well as in those with an ischaemic stroke, are not effective. With the increasing population life expectancy, and prevalence of cardiovascular disease, the prevalence of AF and its complications will increase. Since the risk of stroke related to AF can be reduced significantly by oral anticoagulation, further studies should aim to explore barriers and challenges to effective screening.

Background

Cerebrovascular disease remains one of the leading causes of morbidity and mortality globally. It affects 15 million people annually and is responsible for 5 million deaths per annum, contributing to the growing burden of non-communicable diseases (NCDs) worldwide. (1,2) In South Africa, cerebrovascular disease was the fourth leading cause of death in 2016, responsible for 5.1 % of all deaths - the leading cause of death in individuals 65 years and older. (3) Globally approximately 3% of total health care system resources are dedicated to stroke, indicating that cerebrovascular accidents contribute to a significant economic burden on countries. (4,5) In 2008, Bertram et al., estimated that there are 75 000 strokes in South Africa each year, with 25 000 of these fatal within the first month. (6) The burden of disease due to stroke in 2008 in South Africa was 564 000 disability adjusted life years (DALYs), 17% thereof being contributed by years lived with disability (YLD). (6)

Global estimates suggest that an estimated 80% of strokes are ischaemic, with 20% of all ischaemic strokes being cardio-embolic in nature. (7) Maredza et al., estimates that in the South African setting, 71% are ischaemic, 21% haemorrhagic and the remainder are secondary to other causes, including vasculitis, HIV associated opportunistic infections, space-occupying lesions and trauma. (4,8) Embolisation of a mural thrombus in a patient with atrial fibrillation (AF) is the most common mechanism, and patients with AF have a fivefold increased risk for developing a stroke as well as a twofold increased risk of silent cerebral infarction. (7,9,10) Atrial fibrillation, the most common cardiac arrhythmia worldwide, has an estimated prevalence of 0,5-2% in the general population within western countries, (10,11) with a higher prevalence in males as compared to females. (9,11) Current data, albeit sparse, indicates that the prevalence of AF in developing countries is slightly lower than that of the developed world. (11) Despite this lower prevalence of AF in developing countries, the number of AF related deaths increased by 196% from 1990 to 2013 in Sub-Saharan Africa (SSA), (12) as did the number of deaths from strokes, particularly ischaemic strokes with a 102% increase (12). In the United States, AF accounts for approximately 15% of all strokes, 36% of strokes for individuals aged >80, and up to 20% of cryptogenic strokes. This means that AF accounts for 100,000-125,000 embolic strokes per year, of which more than 20% are fatal. (13)

The presence of AF in patients with newly diagnosed strokes is associated with prolonged hospitalisation, increased persistent disability, greater severity of disease, and elevated healthcare costs. (13–15) In addition to this, strokes that occur in the setting of AF have an increased risk of mortality compared to strokes of other aetiologies (30-day mortality OR, 1.84; 95% CI, 1.04 to 3.27). (9) Stroke severity and in-hospital mortality are also significantly greater in those with AF. (16,17)

There is a paucity of data available reporting on the prevalence of AF in the urban population. With the increasing population life expectancy, and other cardiovascular disease, the prevalence of AF and its complications will likely increase. The aim of this study therefore is to determine the prevalence of

atrial fibrillation (AF) in patients with ischaemic stroke, as confirmed on CT scan, at a district level hospital in the Western Cape, South Africa.

Methods

Study design

This is a descriptive study and data collection occurred retrospectively.

Study setting

This study was conducted at Mitchell's Plain Hospital in Cape Town, South Africa. Mitchell's Plain Hospital is a district hospital in the Mitchell's Plain Health District of the Metro Region, which is approximately 32km from Cape Town's city centre. The hospital serves a population of approximately 750 000 - 800 000, which includes the population of Mitchell's Plain and the greater part of Philippi, a large nearby township. The demographics of Mitchell's Plain comprises of low- to middle-income families of which 90% are coloured, and Philippi which is a low-income community that comprises of 90% black residents.

Study population and sampling

Inclusion criteria: All adult patients (age greater or equal to 18 years of age) who presented to Mitchell's Plain Hospital EC with a clinical diagnosis of a stroke or cerebrovascular accident were eligible for inclusion. A diagnosis of stroke, for the purpose of this study was defined as patients with an ICD-10 code (primary or secondary) of a stroke: ICD-10 chapter: "Diseases of the circulatory system" and the ICD-10 subgroup of "cerebrovascular diseases". Consecutive patients were included for the full study period from 1st April 2017 until 31st March 2018 (1 year). This date was chosen as it marks the commencement of data collection on the electronic patient register, HECTIS (Hospital and Emergency Centre tracking information system).

Exclusion criteria: Ischaemic strokes secondary to causes other than thrombosis or an embolism were excluded, e.g. trauma, meningitis, and space occupying lesions (SOL). Patients diagnosed with transient ischaemic attacks were excluded, as well as patients with ischaemic stroke referred from other departments (internal medicine, surgery, psychiatric unit) – the incidence of these referrals are very low and would have complicated the data collection process. Patients transferred to other hospitals for admission where clinical data were inaccessible, were excluded from this study. Patients who were transferred for a CT scan to a different hospital were however included if the patient subsequently returned to Mitchell's Plain Hospital for admission.

Data collection and management

Data was collected in three phases: Phase 1 identified participants from the electronic patient register HECTIS. A search from within the database was conducted for keywords and ICD-10 codes with a clinical diagnosis of stroke. This included the parent ICD-10 group: "Diseases of the circulatory system" and the subgroup of "cerebrovascular diseases". Demographic data was collated during this phase. Phase 2 involved scrutinizing the PACS (Picture archiving and communication system) database for CT Brain scans reports performed on patients identified from phase 1. The formal CT report, as reported by a qualified radiologist, was used for data collection. The absence of an intracranial bleed, or CT scan features indicative of an ischaemic event (embolic or thrombotic) was used to diagnose an ischaemic stroke. Phase 3 involved the collection of clinical data and demographic details for all patients identified from phase 2, by accessing the electronic database, Enterprise content management (ECM). All patients with a confirmed CT scan diagnosis of an ischaemic stroke were included in this phase. Clinical notes were scrutinised for ECGs and each ECG was independently assessed by the two Emergency Physicians for the presence of AF. Clinical notes, as well as previous ECGs, of patients were assessed to help decide whether the AF is presumed new or existing. In those with existing AF, the anticoagulation plan was documented. Random case files (5%) were cross-checked by the study investigators to ensure that data collection was accurate.

Ethical considerations

Existing data was collected retrospectively, and data was deidentified after the data collection process was completed. Folder numbers were used to track the data collection process through the different phases. This study received ethical clearance from the University of Cape Town Human Research Ethics Committee (HREC: 790/2018)

Data Analysis

This study was powered to analyse the primary outcome variable, prevalence, A sample size calculation suggested a minimum of 196 samples, with precision of 5%, an expected prevalence of 15% and a population size of 800 000. Categorical data was described as proportions/percentages and descriptive statistics. Numerical data was described by median and interquartile range (IQR). A 95% confidence interval (CI) is provided when applicable and statistical significance is defined as a $p<0.05$. Categorical data was compared using the Fisher's exact test or Chi-squared test, depending on the sample size.

Results

During the study period of 12 months, 45 944 patients visited the emergency centre of which 36 028 (78%) were adults. The proportion of adult patients with a diagnosis of stroke was 2%. Of those, 11% met exclusion criteria and 6.5% had stroke mimics. Of the 598 that was included, 22% did not have CT scans. Of the CT confirmed strokes, 88% were ischaemic and 10% of those did not have and ECG performed during the clinical stay. Figure 1 depicts a flow diagram of study participants.

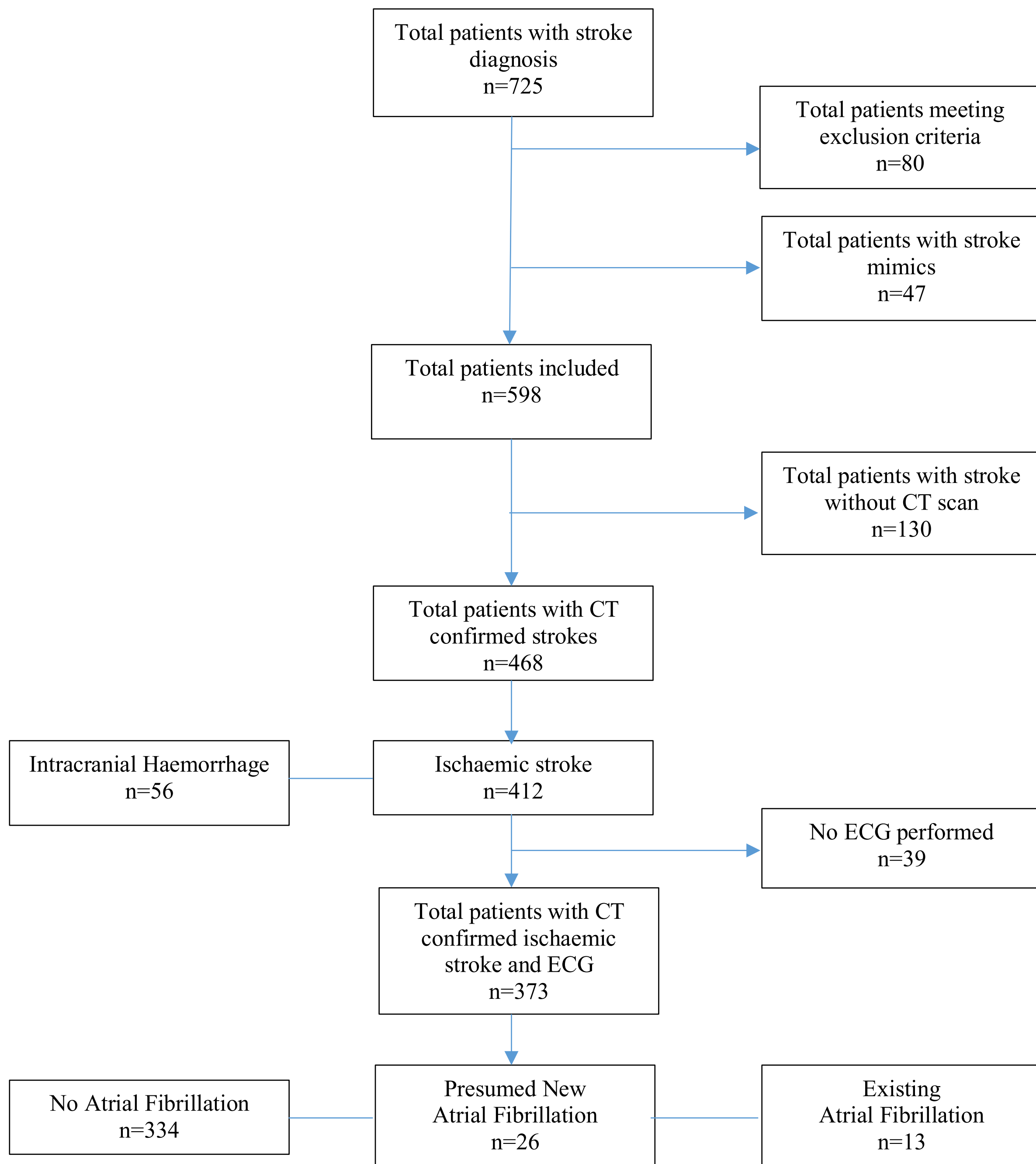

Figure 1: Flow diagram of study participants

11% of all participants with CT confirmed ischaemic strokes had atrial fibrillation, 67% of those presumed new. Of the 13 participants with existing atrial fibrillation, none were therapeutically anticoagulated (Figure 2).

The presence of atrial fibrillation was confirmed by two emergency physicians, who individually evaluated all ECGs (n=373). Initial agreement was achieved in 98.66% of observations with a Cohen's Kappa of 0.931 (95% CI 0.871 to 0.991). The five ECG's that were not agreed upon were discussed and consensus was achieved on all of them, without the need for external validation.

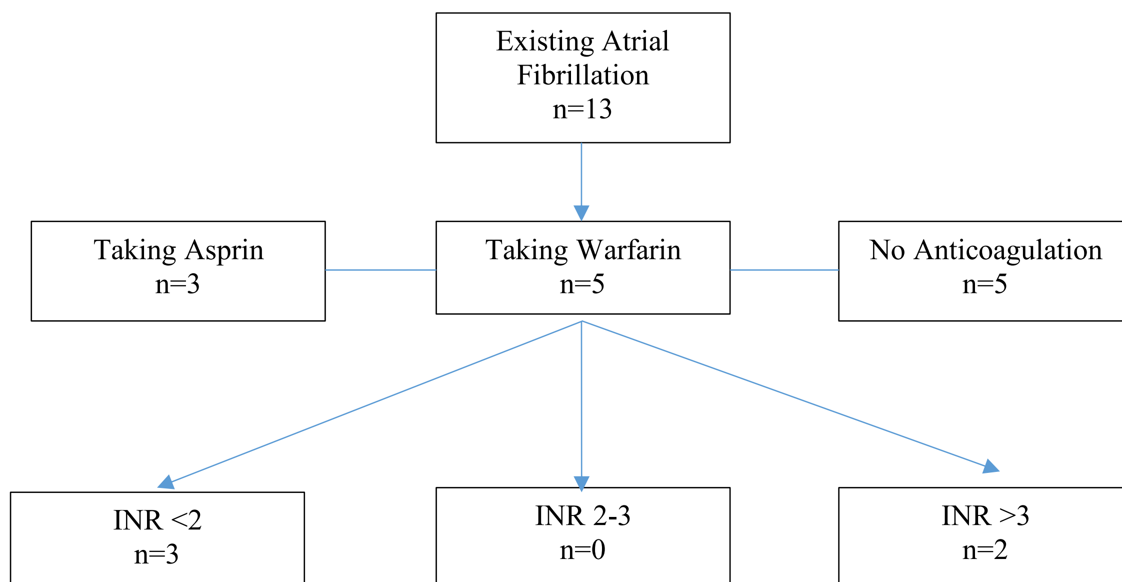

Figure 2: Breakdown of anticoagulation therapy for patients with existing AF

Figure 3 illustrates a scatter plot of the age distribution of participants (n=412) with ischaemic stroke. The graph depicts a normal distribution around a median of 61. The interquartile range is 16 years and 50% of all strokes occurred between 52 and 68 years of age. The youngest participant was 27 years old and the oldest, 99. A total of 90 (22%) of all participants with ischaemic stroke was less than 51 years of age.

Figure 3: Scatter plot of age distribution of participants with ischaemic stroke

The proportion of patients with ischaemic stroke who has atrial fibrillation (n=39) increased significantly from 70 years onwards, as illustrated in Figure 4.

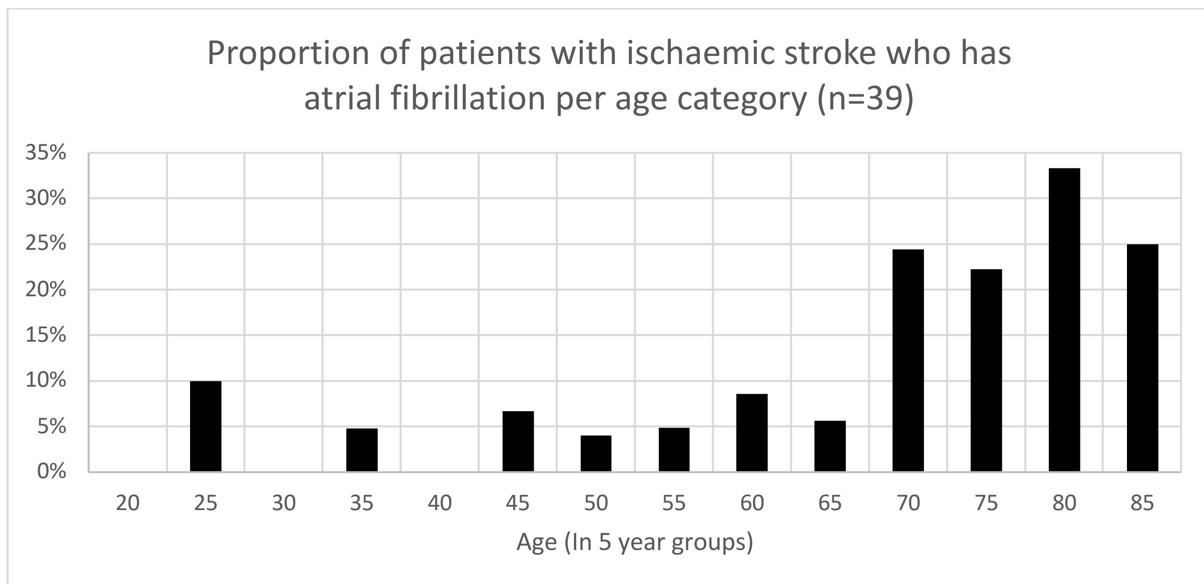

Figure 4: Proportion of patients with ischaemic stroke who has atrial fibrillation per age category (n=39)

Table 1 compares the demographic details of all participants who met inclusion criteria. The p-values were calculated by comparing only participants with ischaemic and haemorrhagic strokes.

Table 1: Demographic details of participants with ischaemic and haemorrhagic stroke

n, (%)	Ischaemic n=412	Haemorrhagic n=56	Other n=47	No CT-scan n=130	p-value
Gender					
Male	209 (51%)	34 (61%)	19 (40%)	72 (55%)	0.199
Female	203 (49%)	22 (39%)	28 (60%)	58 (45%)	
Age					
≤50 years old	90 (22%)	17 (30%)	16 (34%)	18 (14%)	0.175
>50 years old	322 (78%)	39 (70%)	31 (66%)	112 (86%)	
Comorbidities					
Hypertension	320 (77%)	33 (59%)			0.004
Diabetes	159 (36%)	6 (11%)			<0.001
Smoking	118 (29%)	12 (21%)			0.340
HIV positive	39 (9,5%)	5 (9%)			1
Dyslipidaemia	89 (22%)	3 (5,3%)			0.002
Excessive alcohol use	18 (4%)	0			0.148
Valve replacement	7 (1,7%)	1 (1,8%)			1
CT-scan					
In-patient	364 (88%)	56 (100%)	44 (94%)		0.004
Out-patient	48 (12%)	0	3 (6%)		
EC Disposition					
Admitted / Transferred	337 (82%)	49 (88%)	37 (79%)	66 (51%)	0.028
Discharged	74 (18%)	3 (5%)	10 (21%)	57 (44%)	
EC Died	1 (0,2%)	4 (7%)	0	7 (5%)	
Outcome					

Survived to discharge / transfer	375 (91%)	52 (93%)	47 (100%)		0.080
In-patient death	37 (9%)	4 (7%)	0		

The proportion of males and females, as well as young age (≤45 years old), was not statistically different between the two groups. With regards to risk factors, hypertension, diabetes and dyslipidaemia were statistically more prevalent in those who had an ischaemic stroke. Smoking, retroviral status, excessive ethanol use, and prior valve replacement were not statistically different between the two groups. All participants with intracranial bleeds received in-patient CT-scans, in comparison to those with ischaemic strokes where 12% were performed as an out-patients – the difference between the two groups being statistically different. 22% of all participants with ischaemic strokes were discharged from the EC, significantly higher than in the haemorrhagic group. The proportion of patients who survived to hospital discharge was not significantly different.

Table 2 compares the demographic details of participants with ischemic stroke between those who had atrial fibrillation and those who did not. The p-values were calculated by comparing only participants with atrial fibrillation and those without atrial fibrillation.

Table 2: Demographic detail of participants with ischaemic stroke.

n, (%)	Atrial Fibrillation n=39	No Atrial Fibrillation n=334	No ECG n=39	p-value
Gender				
Male	18 (46%)	171 (51%)	20 (51%)	0.613
Female	21(54%)	163 (49%)	19 (49%)	
Age				
≤50 years old	4 (10%)	76 (23%)	10 (26%)	0.097
>50 years old	35 (90%)	258 (77%)	29 (74%)	
Comorbidities				
Hypertension	35 (90%)	260 (78%)	25 (64%)	0.971

Diabetes	12 (30%)	136 (40%)	11 (28%)	0.299
Smoking	6 (15%)	104 (31%)	8 (20%)	0.042
HIV positive	1 (3%)	35 (10%)	3 (8%)	0.153
Dyslipidaemia	5 (13%)	81 (24%)	3 (8%)	0.158
Excessive alcohol use	1 (3%)	15 (4%)	2 (5%)	1
Valve replacement	4 (10%)	3 (0,8%)	0	0.003
CT-scan				
In-patient	36 (92%)	292 (87%)	36 (92%)	0.602
Out-patient	3 (8%)	42 (13%)	3 (8%)	
EC Disposition				
Admitted	36 (92%)	268 (80%)	33 (85%)	0.081
Discharged	3 (8%)	65 (19%)	6 (15%)	
Died	0	1 (0,3%)	0	
Outcome				
Survived to discharge	29 (74%)	310 (92%)	36 (92%)	0.001
In-patient death	10 (26%)	24 (7%)	3 (8%)	

There was no statistically significant difference between the proportion of males and females, as well as young age, between those with atrial fibrillation and those without. Smoking was statistically more prevalent in those without atrial fibrillation, while a prior valve replacement was statistically more prevalent in those participants with atrial fibrillation. The other risk factors have a similar distribution in the two groups. Both EC disposition and the proportion of participants receiving in-patients CT scans, were not significantly different in the two groups. The proportion of patients who died was statistically higher in patients who had AF.

Discussions

The proportion of CT confirmed ischaemic strokes of 88% is higher than international figures where it accounts for 80% of all CVAs. (7,14) Limited data from South African suggests that the number should be closer to 71%. (4) This difference could however be explained by the fact that 20% of patients with a clinical diagnosis of an ischaemic stroke did not receive a CT scan – not an uncommon practice in

resource challenged settings. Chunga et al reports that with regards to emergency access to imaging of the brain, 81% of LMICs had access to CT scans, with 84% of them having 24-hour access to radiology services, compared to HICs with 83% and 98% respectively. (18) Global data on the availability of medical devices in 2014 estimated that the number of CT scan machines per 1 million population as only 0.32 in low-income centres compared with 42 in high-income countries, and neuro-diagnostic tests are often inaccessible or unaffordable to many patients in low-income settings. (19)

HIV, a known risk factor for ischaemic strokes, was present in approximately 10% of cases, close to double seen in HICs, where the incidence of HIV positive patients developing strokes are between 1-5%, although a higher proportion (4–34%) have cerebral ischaemic areas at autopsy. (20) Ischaemic stroke seems to be more frequent than cerebral haemorrhage in patients with HIV, at least in a hospital-based series from sub-Saharan Africa, where it is reported in over 90% of HIV-associated strokes. (20–22) Interestingly enough this is not depicted in this population where an equal percentage was seen in both ischaemic and non-ischaemic CVAs.

The prevalence of AF in patients with ischaemic strokes is 11%, lower than the 15-20% reported by the United States, (13,16) and significantly lower than other HICs, where it is reported as being close to 30%. (23,24) A possible explanation for the lower than expected prevalence in AF, is that our study only assessed ECGs of patients with confirmed ischaemic CVAs on CT scan – excluding those who did not have radiological confirmation (20%). In addition, the majority of patients with no AF only had one ECG, which was done on admission. None had continuous/Holter testing and very few had repeat ECGs during their stay in hospital, thus reducing the probability of detecting intermittent/paroxysmal AF. It should be noted that continuous ECG monitoring for periods of 24 hours or more (secondary screening) in stable patients can approximately double the number of AF cases diagnosed when compared to a single short ECG recording. (25)

Two thirds of those with AF were newly diagnosed on presentation which is often the case, suggesting that primary screening practices are lacking. (16) AF satisfies most of the WHO's criteria for a disease suitable for screening. (26) Current European Society of Cardiology guidelines recommend opportunistic screening for AF by pulse taking or ECG rhythm strip instead of a systematic approach in people more than 65 years of age. (26,27) This single timepoint opportunistic pulse palpation with confirmatory ECG in elderly adults is potentially feasible and beneficial for primary stroke prevention. (28) In a Canadian study by Tarride et al, screening for AF, in seniors greater than 65 years of age during routine appointments with their family physicians, with single lead-ECG is a highly cost effective strategy with an incremental cost per quality-adjusted life-year (QALY) gained of CAD$4788. (29) which equates to R51 200. Although the risk of stroke related to AF can be reduced by 64–70% by oral anticoagulation, underutilisation of this effective treatment and delayed diagnosis remain major obstacles, (26,30) thus screening at primary care level is of utmost importance.

Despite increasing data on community-based AF screening becoming available in recent years, questions remain regarding the most appropriate setting and tools. Large-scale systematic AF screening in the community (>4,000 individuals) have been conducted in different countries and regions with AF detection (new diagnosis of AF) rates ranging from 0.5-5.6 %. (26) However, as revealed in a Hong Kong based screening program, the AFinder programme, utilising interpretable smartphone ECGs to screen for AF, the effectiveness was significantly weakened by the lack of a management pathway, and the number needed to screen (NNS) for one patient receiving appropriate oral anticoagulation for newly diagnosed AF was 671. (26) This was in comparison with a Swedish based screening program, the STROKESTOP study where the NNS was 209 because of a structured follow up. (26,31) Therefore a structured downstream management pathway should be a necessary component of any community AF screening programme. (26)

In many HICs mass AF screening of the general population at primary care has become more feasible with the availability of new tools, especially those capable of producing single-lead smartphone ECGs. (26,32) However the sensitivity and positive predictive value of these automated diagnostic algorithms of any ECG-producing tool has to be high enough to save the intermediate step of interpretation by a doctor. (26)

There were no statically significant gender distribution difference, whereas internationally AF is seen more commonly in males, and male gender being an independent risk factor of AF. (9,11) This could be due to a small sample size, as this study was only powered to detect prevalence. Advancing age is a significant risk factor for the development of AF, and with the increase in life expectancy in HIC the prevalence of AF will be higher compared to this population where the median age of ischaemic strokes were 61 years.

The median age of CVAs in this population was 61 years, half of all the CVAs occurred between 52 and 68 years, and most alarmingly, 22% of all the ischaemic strokes occurred in individuals under the age of 51 years. This alarming number is significantly higher compared to HIC, with a prevalence of 18,1/100 000 in a French population, obtained from the French Stroke Registry, 10,8/100 000 in a Finnish based study and 12,1/100 000 in young Italians. (33,34) A systematic review on the incidence of stroke in young adults was published by Marini et al who analysed 29 studies including 3,589 patients under 45 years of age with first-ever stroke, published between 1980 and 2009. Crude rates ranged from 5.76/100 000 to 39.79/100 000 and standardized rates ranged from 6.14/100 000 to 48.51/100 000. (35) According to Bejot et al, the incidence of young strokes, i.e., patients less than 55 years has increased by 40% between 1994-2012, coupled with an increase in hospitalisation, predominately by the increased rates of ischaemic stokes, as seen in the Mitchell’s Plain population. (34) Possible reasons could reflect changes in the burden of vascular risk factors. A rise in the prevalence of type 2 diabetes mellitus, hypercholesterolemia, hypertension and obesity that has been observed in high-income countries, as

well as LMIC. In addition, cigarette smoking and alcohol abuse are frequent in young people and have tended to increase over time. These classic risk factors coupled by a high rate of rheumatic fever and rheumatic heart disease resulting in valvular heart disease and AF, is an additional risk factor for the development of an ischaemic stroke, with valvular heart disease being statically significant for the development of AF in this population. In addition to all the above HIV could also be a significant risk factor for young CVAs, and further research is required to determine the link between the two particularly in this and other similar settings. Preventive measures are of paramount importance in this young population as it is well documented that the societal impact is high due to the greater number of years of life lost and the resulting loss in productivity. (36)

Anticoagulation is complex, as there are several indications, agents and dosing regimens to choose from. (37) In the South African public healthcare sector, these difficulties are exacerbated by our diverse patient populations, some of whom have multiple comorbidities, and limited access to the various anticoagulants which are available. (37) A fairly recent South African study by Ntlokotsi et al essentially looked at patients with valve replacements, with or without AF, over a 3-year period with the optimum INR target ranges for all participants estimated to be between 2.0– 3.5. (37,38) Alarming though the quality of warfarin anticoagulation of the participants with valve replacement was found to be inadequate as indicated by percentage time in treatment range (TTR) which was 49.7% for all study participants compared with the ideal TTR of 70% and above. (38) Similar results were demonstrated by Sonuga et al, looking at anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. (39) Possible explanations for warfarin's TTR in this study include non-compliance, drug-drug interaction, drug- food interactions and patient comorbidities. (37,40) All these complexities are found in our population.

The most significant limitation of this study is that it may not represent the true prevalence of AF in patients with ischaemic CVAs due to the following factors: (i) sampling excluded patients who presented to primary health care facilities and/or those who were discharged from these facilities; (ii) sampling excluded patients who died before reaching the hospital; (iii) sampling did not include all patients who are referred to tertiary facilities; (iv) patients who have paroxysmal AF may have been missed by routine screening practices and (vi) the data collection process was retrospective and dependant on clinical notes and accurate record keeping, and lastly (vii) the prevalence of AF in ischaemic CVA may be somewhat misleading as 10% of the ischaemic CVA patients did not have an ECG. Selection bias may further influence the results because of the fact that only 80% of included patients had a CT scan. This may have skewed the data towards the null value, considering that patients with embolic/ischaemic strokes often present much more benign than those with intracranial haemorrhage. This could have led to an underestimation of the prevalence of AF in ischaemic CVA's.

Anticoagulation and screening practices may not represent the greater Western Cape community and may reflect district or institution specific practices.

Future research should attempt to calculate the true prevalence of atrial fibrillation in patients with ischaemic strokes, practically involving a multicentre data collection model across different levels of care. A standardised protocol and clerking sheet will also provide more information and provide cognitive checks to perform minimum investigations. The reasons and barriers for the limited primary and secondary screening for atrial fibrillation should be sought and addressed.

Conclusions

Atrial fibrillation is a major risk factor for developing ischaemic cerebrovascular accidents. With the increasing population life expectancy, and other cardiovascular disease, the prevalence of AF and its complications will increase. Although the risk of stroke related to AF can be reduced significantly by oral anticoagulation, delayed diagnosis and ineffective screening practices remain major obstacles. This study confirms that a significant proportion of patients with an ischaemic stroke have undiagnosed AF and that secondary screening of those with an ischaemic stroke is challenging. It is paramount that all patients that present with CVAs receive at least an ECG on admission and perhaps prior to discharge. Since atrial fibrillation is a modifiable risk factor, further studies should aim to explore barriers and challenges to effective screening. Another important discovery from this study is that there is a high proportion of patients with "young CVAs". This was not the main focus of this study but definitely needs to be investigated and more research is needed to identify why this is so and why the prevalence of young CVAs are increasing.

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Competing interests and funding

The authors declare no competing interest and the study was self-funded.

Author contributions

MM, CH and KV developed the concept. CH and MM constructed the proposal. CH was responsible for the ethical clearance and facility approval. KV and MM prepared the literature review. MM and CH performed the data collection and CH the data analysis. CH, MM and KV contributed to the final article.

References

1. Wolfe CDA. The impact of stroke. British Medical Bulletin. 2000;56(2):275-286. Avaiable on website https://doi.org/10.1258/0007142001903120

2. Observatory GH. Deaths from NCDs. 2008; World Health Organization. Deaths from NCDs. Available from website http://www.who.int/gho/ncd/mortality_morbidity/ncd_total/en/, year 2008

3. StatsSA. Mortality and Causes of Death in South Africa , 2006 : Findings from Death Notification. Mortality [Internet]. 2008;(June):1–74. Available from: http://www.statssa.gov.za/Publications/P03093/P030932006.pdf

4. Maredza M, Chola L, Economic burden of stroke in a rural South African setting, MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. 2017;26–32.

5. Antonio Di Carlo, Human and economic burden of stroke, Age and Ageing, 2009;(January)38(1):4–5. Available from: https://doi.org/10.1093/ageing/afn282

6. Bertram MY, Katzenellenbogen J, Vos T, Bradshaw D, Hofman KJ. The disability adjusted life years due to stroke in South Africa in 2008. Int J Stroke. 2013;8(100 A):76–80.

7. Marx JA, Hockberger RS, Walls RM. Rosen's Emergerncy Medicine, Concepts and Clinical Practice, 8th Edition. 2014. 1363-1374 p.

8. Bryer A, Connor MD, Haug P, Cheyip B, Staub H, Tipping B, et al. GUIDELINE South African, guideline for management of ischaemic stroke and transient ischaemic attack 2010 : A guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. 2010;100(11).

9. Magnani JW, Rienstra M, Lin H, Sinner MF, Lubitz S a, Mcmanus DD, et al. Atrial fibrillation: Current knowledge and future directions in epidemiology and genomics. Circulation. 2011;124(18):1982–93.

10. Huisman M V., Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 2017;69(7):777–85.

11. Fan X, Zhang S. The Optimal Treatment For Atrial Fibrillation In Less Developed Countries. JAFIB J Atr Fibrillation [Internet]. 2014;7(3). Available from: http://www.jafib.com/published/webFormat/Shu_Zhang/shu_zhang.pdf

12. Mensah GA, Roth GA, Sampson UK, Moran AE, Feigin VL, Forouzanfar MH, Naghavi M, Murray CJ, . Mortality from cardiovascular diseases in sub-Saharan Africa, 1990-2013: A systematic analysis of data from the Global Burden of Disease Study 2013 [Internet]. Vol. 26, Cardiovascular Journal of Africa. 2015. p. S6–10.

13. Reiffel JA. Atrial Fibrillation and Stroke: Epidemiology. Am J Med [Internet]. 2014;127(4):e15–6.

14. Di Giosia P, Giorgini P, Ferri C. Considerations on stroke in atrial fibrillation despite anticoagulation. J Cardiovasc Med [Internet]. 2018;19(suppl 1):e54–7. Available from: http://insights.ovid.com/crossref?an=01244665-201802001-00014

15. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11(11):639–54.

16. Andrew NE, Thrift AG, Cadilhac DA. The prevalence, impact and economic implications of atrial fibrillation in stroke: What progress has been made? Neuroepidemiology. 2013;40(4):229–39.

17. Huey-Juan L, A. WP, Margaret K-H, S. BA, S. KC, J. BE, et al. Stroke Severity in Atrial Fibrillation. Stroke [Internet]. 1996 Oct 1;27(10):1760–4. Available from: https://doi.org/10.1161/01.STR.27.10.1760

18. Chunga R, Bruijns SR, Hendrikse C. African Journal of Emergency Medicine Access to acute care resources in various income settings to treat new-onset stroke : A survey of acute care providers. African J Emerg Med [Internet]. 2019;(January):1–4. Available from: https://doi.org/10.1016/j.afjem.2019.01.002

19. Berkowitz A, Stroke A. Managing acute stroke in low-resource settings, *Bulletin of the World Health Organization,* December 2016; 94:554-556.
doi: http://dx.doi.org/10.2471/BLT.15.162610

20. Benjamin LA, Bryer A, Emsley HCA, Khoo S, Solomon T, Connor MD. HIV infection and stroke: current perspectives and future directions. Lancet Neurol [Internet]. 2012 Oct;11(10):878–90. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22995692

21. Ortiz G, Koch S, Romano JG, Forteza AM, Rabinstein AA. Mechanisms of ischemic stroke in HIV-infected patients. Neurology [Internet]. 2007 Apr 17;68(16):1257 LP-1261. Available from: http://n.neurology.org/content/68/16/1257.abstract

22. Mochan A, Modi M, Modi G. Protein S deficiency in HIV associated ischaemic stroke: an epiphenomenon of HIV infection. J Neurol Neurosurg Psychiatry [Internet]. 2005 Oct;76(10):1455–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16170096

23. Bjorn-Mortensen K, Lynggaard F, Pedersen ML. High prevalence of atrial fibrillation among Greenlanders with ischemic stroke - Atrial fibrillation found in more than 30% of cases. Int J Circumpolar Health. 2013;72(1):2–4.

24. Friberg L, Rosenqvist M, Lindgren A, Terént A, Norrving B, Asplund K. High Prevalence of Atrial Fibrillation Among Patients With Ischemic Stroke. Stroke. 2014;45(9):2599–605. Available from: http://stroke.ahajournals.org/lookup/doi/10.1161/STROKEAHA.114.006070

25. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of Ambulatory 7-Day ECG Monitoring for the Detection of Atrial Fibrillation and Flutter After Acute Stroke and Transient Ischemic Attack. Stroke. 2004;35:1647–1651

26. Chan N-Y. Systematic Screening for Atrial Fibrillation in the Community: Evidence and Obstacles. Arrhythmia Electrophysiol Rev. 2018 Mar;7(1):39–42. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29636971

27. Fitzmaurice DA, Hobbs FDR, Jowett S, Mant J, Murray ET, Holder R, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. BMJ. 2007 Aug 25;335(7616):383. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17673732

28. Yang D. Should patients undergo atrial fibrillation screening for primary stroke prevention ?; Clinical Correlations; 26 July 2018; Available from website https://www.clinicalcorrelations.org/2018/07/26/should-patients-undergo-atrial-fibrillation-screening-for-primary-stroke-prevention/

29. Tarride J, Quinn FR, Blackhouse G, Sandhu RK, Burke N, Gladstone DJ, et al. Training / Practice Health Policy and Promotion Is Screening for Atrial Fibrillation in Canadian Family Practices Cost-Effective in Patients 65 Years and Older ? Can J Cardiol [Internet]. 2018;34(11):1522–5. Available from: https://doi.org/10.1016/j.cjca.2018.05.016

30. Haeusler, K.G., Tütüncü, S. & Schnabel, R.B. Curr Neurol Neurosci Rep, Detection of Atrial Fibrillation in Cryptogenic Stroke. (2018) 18: 66:1-7. Available from https://doi.org/10.1007/s11910-018-0871-1

31. Svennberg E, Engdahl J, Al-khalili F, Friberg L, Frykman V. Mass Screening for Untreated Atrial Fibrillation, The STROKESTOP Study; Arrhythmia/Electrophysiology. CirculationAHA. June 1, 2015;131:2176–2184. Available on https://doi.org/10.1161/CIRCULATIONAHA.114.014343

32. Karmen CL, Reisfeld MA, McIntyre MK, Timmermans R, Frishman W. The Clinical Value of Heart Rate Monitoring Using an Apple Watch. Cardiol Rev [Internet]. 9000;Publish Ahead of Print.Available from: https://journals.lww.com/cardiologyinreview/Fulltext/publishahead/The_Clinical_Value_of_Heart_Rate_Monitoring_Using.99708.aspx

33. Smajlovic D. Strokes in young adults : epidemiology and prevention. Dove Press; February 24, 2015; Volume 2015:11, pages 157–64.

34. Delpont B, Giroud M, Sample NI, Dijon T. Registry S. Rising Stroke Incidence in Young Adults : More Epidemiological. 2010;1–3.

35. Marini C, Russo T, Felzani G. Incidence of stroke in young adults: a review. Stroke Res Treat [Internet]. 2010 Dec 19;2011:535672. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21197401

36. Krishnamurthi R V., Moran AE, Feigin VL, Barker-Collo S, Norrving B, Mensah GA, et al. Stroke Prevalence, Mortality and Disability-Adjusted Life Years in Adults Aged 20-64 Years in 1990-2013: Data from the Global Burden of Disease 2013 Study. Neuroepidemiology. 2015;45(3):190–202.

37. Laäs DJ, Chb MB, Naidoo M, Chb MB, Medicine S. Oral anticoagulants and atrial fibrillation : A South African perspective. 2018;108(8):640–6.

38. Ntlokotsi S, Moshesh MF, Mntla P, Towobola OA, Mogale MA. Optimum INR intensity and therapeutic INR control in patients with mechanical heart valve prosthesis on warfarin oral anticoagulation at Dr George Mukhari academic hospital : a three-year retrospective study Optimum INR intensity and therapeutic INR control in patients with mechanical heart valve prosthesis on warfarin oral anticoagulation at Dr George Mukhari academic hospital : a three-year retrospective study. Journal of South African Family Practice, Vol 60, No 6 (2018); pg 192-196.

39. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. African J Prim Heal care Fam Med. 2016;8(1):e1–8.

40. Granger CB, Alexander JH, McMurray JJ V, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med [Internet]. 2011 Aug 27;365(11):981–92. Available from: https://doi.org/10.1056/NEJMoa1107039

Part C: Addenda

Addendum 1: Acknowledgements

The investigators have no acknowledgements to declare.

Addendum 2: Author Guidelines (South African Medical Journal)

http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Addendum 3: Research Proposal

Dissertation Proposal

The prevalence of atrial fibrillation in patients with ischaemic stroke in a district hospital in the Western Cape.

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This study is in partial fulfilment of the Master of Medicine (Emergency Medicine) degree

Declaration

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List of Abbreviations

AF	Atrial fibrillation
CI	Confidence interval
CT	Computed tomography
CVA	Cerebrovascular accidents
CHC	Community health centres
DALYs	Disability adjusted life years
EC	Emergency Centre
ECG	Electrocardiogram
ECM	Enterprise content management (electronic medical records)
GSH	Groote Schuur Hospital
HECTIS	Hospital and Emergency Centre tracking information system
HIC	High-Income Country
IQR	Interquartile range
LMIC	Low- and Middle-Income Country
MPH	Mitchells Plain Hospital
MRI	Magnetic resonance imaging
PACS	Picture archiving and communication system
SD	Standard deviation
SSA	Sub-Saharan Africa
UCT	University of Cape Town
YLD	Years lived with disability

Abstract

Introduction

Stroke remains one of the leading causes of morbidity and mortality worldwide, affecting both high- and low- to middle-income countries alike, resulting in an immeasurable human, economic and societal burden. In South Africa, cerebrovascular disease was the fourth leading cause of death in 2016, responsible for 5.1 % of deaths, and the leading cause of death in individuals 65 years and older. In high-income countries, AF accounts for approximately 15% of all strokes, but there is however a paucity of data available on the prevalence of atrial fibrillation in stroke in South Africa. This study sets out to determine the prevalence of atrial fibrillation in patients with strokes, as confirmed on CT scan, in a district level hospital in the Western Cape, South Africa.

Methodology

This descriptive study will be conducted at Mitchells Plain Hospital in Cape Town and data will be collected for a year. Patients diagnosed with a stroke will be identified from the electronic patient register and relevant radiology and clinical data will be sourced from the various electronic databases. CT scan reports will determine the diagnosis of an ischaemic stroke and ECG's will be independently screened for atrial fibrillation by two emergency physicians. A 95% confidence interval (CI) will be provided and statistical significance will be defined as a $p<0.05$.

Ethical Considerations

The research project will de-identify the data in the very beginning of the data collection period and therefore poses minimal risk to the participants. Data will also be aggregated, and no individual data will be published and reported on. By including the clinical data of participants, it will in no way affect the rights and welfare of participants. A waiver of written consent will therefore be applied for. Ethical approval will be obtained from the Human Research Ethics Committee of the University of Cape Town. Thereafter, institutional approval will be obtained from Mitchell's Plain Hospital.

Conclusions

This is one of the first studies of its kind in the Western Cape and a reasonably big study with regards to number of participants and power of measurements. The study will provide insight into the prevalence of atrial fibrillation in patients with strokes in an urban setting. Information from this study

should be used to adopt screening tools for atrial fibrillation, early risk stratification assessments and facilitate the appropriate use of anticoagulation to prevent cardioembolic ischaemic strokes.

Introduction

Background

Stroke, also known as cerebrovascular accident (CVA), is defined as a neurologic deficit caused by a cerebrovascular problem which persist for more than 24 hours or causes death within 24 hours. (1) It is characterised by focal or global cerebral functional impairment, affecting both motor and sensory function, and rapidly evolving. (1)

Cerebrovascular disease remains one of the top causes of morbidity and mortality worldwide, both in high-income countries (HICs) and low- and middle-income countries (LMICs). (2) In South Africa cerebrovascular disease was the fourth leading cause of death in 2016, responsible for 5.1 % of deaths (3) , and the leading cause of death in individuals 65 years and older. (3) Globally approximately 3% of total health care system resources are dedicated to stroke indicating that cerebrovascular accidents composes a significant economic burden on countries. (4,5) There is a paucity of local data that describes the financial impact that stroke care and resources utilised, amount to. Maredza et al., it is stated that the "total direct costs of strokes were estimated to be 2.5-4.2 million in the year 2012 in a small rural community in South Africa". (4). This analysis is based on a population of approximately 90,000 people residing in the Agincourt sub-district of Mpumalanga province, north-east of South Africa. (4)

In 2008, Bertram et al., estimated that there are 75 000 strokes in South Africa each year, with 25 000 of these fatal within the first month. (6) The burden of disease due to stroke in 2008 in South Africa was 564 000 Disability adjusted life years (DALYs). Of this, 17% is contributed by Years lived with disability (YLD). (6)

In 2008 in the United States the total direct and indirect costs of stroke was estimated to cost the economy an estimated 65.5 Billion dollars, where the indirect costs incurred were due to loss of productivity resulting from morbidity and mortality. (5) In addition to this, informal care, which is often overlooked, remains of utmost importance to maintain stroke survivors in the community resulting in an additional economic and social burden. (5)

Fifteen percent of stroke survivors require long-term institutional care, while 70% are left with significant physical, emotional or cognitive impairment, such as depression, anxiety, communication difficulties, gainful enjoyment and dementia. (7) The need of support for common daily activities and social integration directly impacts quality of life of patients and their relatives, who frequently take on the role of caregivers. (5,7)

An estimated 80% of strokes globally are ischaemic in nature, and the rest non-ischaemic, either being haemorrhagic or secondary to a different cause. (2) Maredza et al., estimates that in the South African setting 71% are ischaemic, 21% being haemorrhagic and the remainder secondary to a different cause.

(4) International data states that one fourth of all ischaemic strokes are cardio-embolic in nature. (1,2) Embolization of a mural thrombus in a patient with atrial fibrillation (AF) is the most common mechanism, and patients with AF have a fivefold increased risk for developing a stroke. (2,8,9) In addition to this, the presence of AF in patients with newly diagnosed strokes is associated with prolonged hospitalisation, increased persistent disability and elevated healthcare costs. (1,10,11)

Atrial fibrillation (AF), the most common cardiac arrhythmia worldwide, has an estimated prevalence of 0,5-2% in the general population within western countries (9,12), with a higher prevalence in males compared to females. (8,12) Current data, albeit sparse, indicate that the prevalence of AF in developing countries are slightly lower to that of developed world. (12) Despite this lower prevalence of AF in developing countries the number of AF related deaths increased 196% from 1990 to 2013 in Sub-Saharan Africa (SSA) (13), as did the number of deaths from strokes, particularly ischaemic strokes with a 102% increase. (13) As AF becomes more prevalent with age, the incidence of AF is estimated to increase progressively in the future with the increased mortality and morbidity associated with it. (12)

In the United States AF accounts for approximately 15% of all strokes, 36% of strokes for individuals aged >80, and up to 20% of cryptogenic strokes. (11) This means that AF accounts for 100,000-125,000 embolic strokes per year, of which more than 20% are fatal. (11)

Data on the general prevalence and incidence of AF in Africa are sparse, particularly in South Africa with small studies estimating it to be 5.6 cases per 100000 per year (14), with nil data available about the prevalence of AF in patients with ischaemic strokes in an urban environment.

Motivation

Atrial fibrillation is a major risk factor for developing ischaemic cerebrovascular accidents, as well as other cardio-embolic complication, particularly in our urban environments. There is a paucity of data available reporting on the prevalence of AF in the urban population, particularly in patients with CVAs. With the increasing population life expectancy, and other cardiovascular disease, such as hypertension, diabetes, congestive cardiac failure and valvular heart disease the prevalence of AF is sure to increase, as well as its complications.

This study will help to provide much needed information about the prevalence of AF in this particular population, as well as other demographics of CVAs. The results of which can be used to adjust hospital protocols, hospital and community screening of AF, early risk stratification and early initiation of anticoagulants to prevent the cardio-embolic complications of AF, particular CVAs. With an overall reduction in patient mortality and morbidity and a decrease in economic burden associated with CVAs and other AF related complications.

Aims

To determine the prevalence of atrial fibrillation (AF) in patients with ischaemic cerebrovascular accidents, as confirmed on CT scan, in a district level hospital in the Western Cape, South Africa.

Objectives

1. To calculate the proportion of patients presenting to the EC with a suspected stroke.
2. To stratify all clinically suspected strokes into CT diagnosis (haemorrhagic vs ischaemic vs other) and to describe the demographics for each category.
3. To determine the prevalence of atrial fibrillation in patients with confirmed ischaemic stroke and to establish whether it is presumed new or existing.
4. To describe the anticoagulation treatment plan of patients with existing AF.
5. To calculate the proportion of patients on Warfarin that are therapeutic or sub-therapeutic.

Methodology

Study design

This is a descriptive study collecting data as a retrospective chart review.

Study setting

This study will be conducted at Mitchells Plain Hospital in Cape Town, South Africa. Mitchell's Plain Hospital is a district hospital in the Mitchell's Plain Health District of the Metro Region, which is approximately 32km from Cape Town's city centre. The hospital serves a population of approximately 750 000 - 800 000, which includes the population of Mitchells Plain and the greater part of Philippi, a large nearby township. The demographics of Mitchells Plain comprises of low- to middle-income families of which 90% are coloured, and Philippi which is a low-income community that comprises of 90% black residents.

Study population and sampling

Inclusion criteria

1. Adult patients (age greater or equal to 18 years of age) who presented to Mitchell's Plain Hospital EC with a clinical diagnosis of a stroke or cerebrovascular accident. A diagnosis of stroke for the purpose of this study is defined as patients with an ICD-10 code (primary or secondary) of a stroke: ICD-10 chapter: "Diseases of the circulatory system" and the ICD-10

subgroup of "cerebrovascular diseases". All patients that meet the above-mentioned criteria will potentially be eligible for inclusion.

2. Serial/consecutive patients will be included for the full study period.
3. The data collection period is for 1 year and from 1st April 2017 until 31st March 2018. This date was chosen as it marks the commencement of data collection on the electronic patient register, HECTIS (Hospital and Emergency Centre tracking information system)

Exclusion criteria

1. Patients transferred to other hospitals for admission, where clinical notes would be inaccessible will be excluded from this study – patients who are referred for a CT scan at a different hospital (GSH) will be included if the patient subsequently returns to Mitchell's Plain Hospital for admission.
2. Ischaemic strokes secondary to causes other than thrombosis or an embolism will be excluded, e.g. in trauma, meningitis, etc.
3. Patients diagnosed with transient ischaemic attacks.
4. Patients with CVAs referred from other departments (internal medicine, surgery, psychiatric unit) – the incidence of these referrals is very low and would complicate the data collection process.

Data collection and management

Data will be collected in three consecutive phases:

Phase 1:

Participants will be identified from the electronic patient register HECTIS. A search from within the database will be conducted for keywords and ICD-10 codes with a clinical diagnosis of stroke. This will include the parent ICD-10 group: "Diseases of the circulatory system" and the subgroup of "cerebrovascular diseases". All patients that meet the above-mentioned criteria will potentially be eligible for inclusion. Demographic data will be collected from HECTIS and the folder numbers will be the only identifying variable that will be included at this stage. It will be necessary to link the first, second and third stages of the data collection period.

Phase 2:

The PACS (Picture archiving and communication system) database will then be scrutinised for CT Brain scans performed on patients identified from phase 1. The formal CT report, as diagnosed by a qualified radiologist, will be used for data collection. The absence of an intracranial bleed, or CT scan features indicative of an ischaemic event (embolic or thrombotic) will be used to diagnose an ischaemic

stroke. It is expected that a few patients may have received CT scans at a referral hospital (Groote Schuur (GSH) as Mitchells Plain Hospital does not have after hour CT scan services). Groote Schuur Hospital's PACS system will then be searched for CT scan reports.

Phase 3:

The electronic database, ECM, will be scrutinised for all patients identified from phase 2 of the data collection process. All patient with a confirmed CT scan diagnosis (or strong suspicion) of an ischaemic stroke will be included in this phase. Demographic details and comorbid conditions will be collected but no personal identifying information will be included. At this stage of the study, all data will be de-identified by linking it with a study number.

Patients clinical notes will be searched for ECG's. All ECG's will be assessed independently by the two project supervisors who are emergency physicians for the presence of AF. All ECG assessments that differed between the two emergency physicians will be discussed to reach consensus. A third expert (cardiologist) will be consulted if consensus cannot be reached. Clinical notes, as well as previous ECGs, of patients will be assessed for whether the AF is presumed new or existing. In those with existing AF, the anticoagulation plan will be assessed, as well as whether the participant is on Warfarin (therapeutic or not), Aspirin or on no anticoagulation. A graphical representation of the data-collection process can be found below:

Missing data or incomplete records:

Cases will be excluded if patients' clinical data or information is missing or inaccessible. The number of missing cases will be clearly described and as well as much as possible of the relevant descriptive details (demographics, etc.). This will allow for comparison between cases and missing data. The investigators will make every effort to prevent missing data, including meeting with ECM of PACS administrators to try and minimise missing / lost data. A flow chart of cases and missing data/incomplete records will be presented.

Because this will be a descriptive study and because it will not be testing a hypothesis, incomplete data will be included and described up to the point where it can no longer be analysed. This will clearly be documented and described. Demographics will be presented for both missing and incomplete data so that it can be compared to those with complete data. The expected effect is described in the limitations section.

In those cases where the analysis of clinical data provides uncertain information, it will be presented as "unsure" and not categorised into a definitive category, for example if unsure whether AF is presumed new or existing.

Variables and data sources:

Phase 1

Source: HECTIS

Variables: Folder number; Gender; Age; ICD-10 diagnosis; date of admission

Phase 2

Source: PACS

Variables: CT performed - yes or no; date of CT scan; diagnosis (3 categories)

Phase 3

Source: ECM

Variables: comorbid diseases; ECG present or not; ECG diagnosis AF or not (Specialist 1); ECG diagnosis AF or not (Specialist 2); AF presumed new or existing; Anticoagulation plan or no treatment plan; Warfarin or not; Aspirin or not; INR level (if on Warfarin);

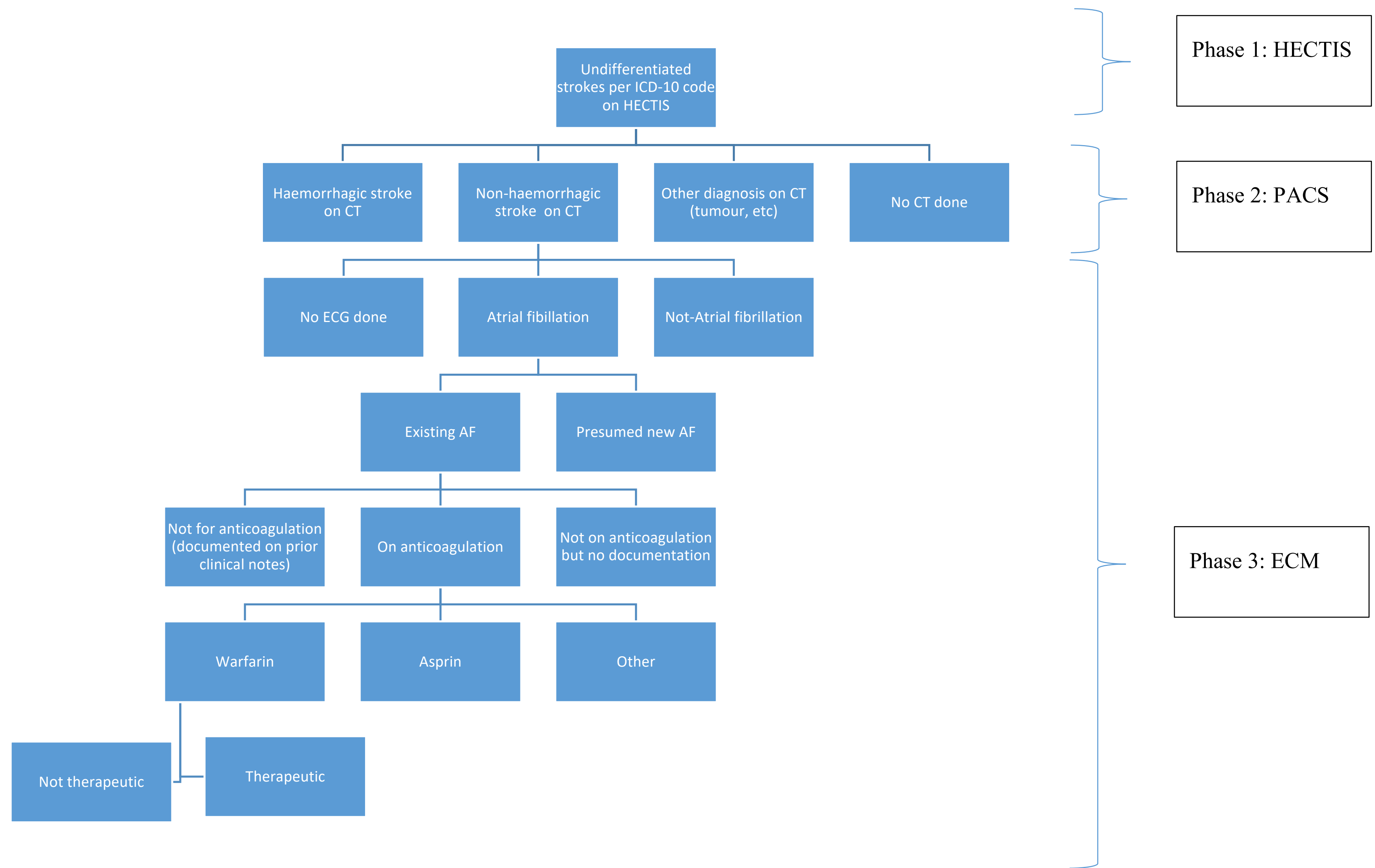

Figure 5: Proposed structure of data collection

Data safety and monitoring

Care will be taken to protect the identity of each patient. No identifying data will be collected. Initially the patients folder number will be obtained from the PACS database (which will be necessary to tract the patients ECM records), thereafter the demographics and clinical data will be collected. The data will be de-identified from this step onwards. A study number will be given to each patient and thereafter only study numbers will be used. Names and folder numbers will be saved against study numbers in a separate file in cases of a query. Only study personnel will have access to the files and it will be password protected and saved in a university computor at UCT, which will also be password protected. Also, information obtained will be backed up in a cloud server which will also be password protected and accessed only by study investigators.

Data Analysis

For this study to be powered to measure prevalence, a minimum of 246 samples are required, if we accept a precision of 5%, an expected prevalence of 20% and a population size of 600 000. An informal audit revealed an estimate of 60 undifferentiated strokes per calendar month presents to Mitchell's Plain Emergency Centre. Considering the fact that not all strokes are ischaemic, data over a one-year period will provide a sufficient sample size to mitigate for this. Categorical data will be described in percentages and descriptive statistics. Continuous variables will be described by mean +/- standard deviation (SD) or median and interquartile range (IQR). A 95% confidence interval (CI) will be provided and statistical significance will be defined as a $p<0.05$. Categorical data will be compared using the Fisher's exact test or Chi-squared test, depending on the sample size. Continuous variables will be compared with the t-test or Mann-Whitney test as appropriate.

Ethical considerations

Risk to patients

Routine clinical data will be collected retrospectively from folders and the electronic database, ECM. Extracting data from an existing database essentially renders it a large-scale clinical folder audit and patient care will thus not be affected in any way. The research project will de-identify the data in the very beginning of the data collection period and therefore poses minimal risk to the participants. Data will also be aggregated, and no individual data will be published and reported on. By including the clinical data of participants, it will in no way affect the rights and welfare of participants. A waiver of written consent will therefore be applied for.

In the event of a missed clinical diagnosis that has become evident during the data collection period, the relevant clinician or clinical team will be informed as soon as possible, for example undiagnosed atrial fibrillation.

Risk to community

This project will only benefit the community of Mitchell's Plain. It may become the basis of future research to improve the plight of the at-risk population with regards to minimising stroke prevalence in AF. This study poses no risk to the community.

Risk to clinician

No data specific to any clinician will be collected.

Risk to institution

This study poses no risk to Mitchell's Plain Hospital.

Ethical approval will be obtained from the Human Research Ethics Committee of the University of Cape Town. Thereafter, institutional approval will be obtained from Mitchell's Plain Hospital.

There will be no reimbursement for participation.

Limitations and strengths

Strengths

This is one of the first studies of its kind in the Western Cape and a reasonably big study with regards to number of participants and power of measurements. The information gained from this study could form the basis for future studies to help decrease the prevalence of embolic stroke in patients with AF.

Limitations

The study may not represent the true prevalence of AF in patients CVAs due to the fact:

1. Sampling does not include patients who present to community health centres or general practitioners and/or those who were discharged from these facilities and subsequently not referred to district hospitals
2. Sampling does not include patients who died before reaching the hospital
3. Sampling does not include those patients who are referred to tertiary facilities
4. It may be difficult to distinguish between embolic and thrombotic CVAs on CT scans

5. Those patients who have paroxysmal AF may be missed by our screening, yet the risk of embolic CVAs and other cardio-embolic events are the same as those with chronic AF.
6. Patients with existing AF will be defined as a clinical documentation of the presence of AF in historic notes, whether in the clinical notes, discharge summaries or whether it was documented as ICD-10 code on previous episodes.

Selection bias my influence results if not all patients receive CT scans of the brain. This may lead to skewed data, considering that patients with embolic/ischaemic strokes often presents much more benign clinically than those with intracranial bleeds. Many patients with ischaemic/embolic strokes may therefore not have had a CT scan, and this may skew the effect towards the null value. A larger sample my therefore be necessary in an attempt to mitigate this potential source of bias.

Anticoagulation and screening practices may not represent the greater Western Cape community and may reflect district or institution specific practices.

It is fair to expect missing or incomplete data, due to the fact that this is a retrospective study. Even though the investigator will clearly describe and present the demographics of the missing / incomplete data, it may affect the outcome and conclusion if the number of missing data if significant (>5%). This potentially will result in a smaller sample size and therefore decrease the power of the study, introducing a selection bias. The investigator will try to prevent missing or incomplete data as far as possible. Missing or incomplete data will be presented in as much as possible detail, to allow for comparison with cases.

Data dissemination plan

Publication in a peer review journal is expected.

The study will provide insight to the prevalence of AF in those patients with cerebrovascular disease in an urban hospital within Cape Town. Further studies could build from it, ultimately to establish early screening tools for AF, early risk stratification and the appropriate use of anticoagulation to prevent cardioembolic ischaemic strokes as well as other AF associated cardioembolic events. The results obtained from this study will be presented to the hospital and other hospitals in the substructure so that they can plan and improve services. This could result in protocol change and could suggest a need for training and upskilling of clinicians, e.g. if a very high proportion of AF is undiagnosed, screening programs should be improved. And if those with AF have subtherapeutic anticoagulation therapies, it could suggest improved monitoring at a primary health care level.

Project Time Line

Table 3: Project timeline

2018	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***July***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
EMDRC					X	X						
Ethics						X	X					
Hospital Permission								X	X			
Data Collection										X	X	
Data Analysis												X
2019	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***July***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Writeup	X	X	X									
Submission				X	X							

Resources and budget

Hardware: Laptop, Hard drive- available, nil cost

Software: Word processing software, referencing software, data management software and statistcal analysis software- available, nil cost

The total budget of R1300 will be carried by the research team.

Table 4: Budget

May 2018 – July 2019				
Item	**Description**	**Unit cost**	**Nº of Units**	**Total cost**
Consumables				
1. materials and supplies				
2. materials and supplies				
3. specialised services				
4. office supplies, printing & reproduction for data collection	Stationary-pens, notepads, files			R500
5. office supplies, printing & reproduction for reports	Printing-data collection, reports, paper			R300

Research travel				
1. travel to sites	Travel to MPH: x 5 trips = 30km x 10 = 300km = +/-R400 (SARS rates)			R400
2. other, specify	Travel to UCT library: 5 trips= 5km x 10= 50km			R100
Minor research equipment				
1.				
2.				
3.				
Sub-Total				
Total				**R1300**

Reference:

1. Di Giosia P, Giorgini P, Ferri C. Considerations on stroke in atrial fibrillation despite anticoagulation. J Cardiovasc Med [Internet]. 2018;19(suppl 1):e54–7. Available from: http://insights.ovid.com/crossref?an=01244665-201802001-00014

2. Marx JA, Hockberger RS, Walls RM. Rosen's Emergerncy Medicine, Concepts and Clinical Practice, 8th Edition. 2014. 1363-1374 p.

3. StatsSA. Mortality and Causes of Death in South Africa , 2006 : Findings from Death Notification. Mortality [Internet]. 2008;(June):1–74. Available from: http://www.statssa.gov.za/Publications/P03093/P030932006.pdf

4. Maredza M, Chola L, Economic burden of stroke in a rural South African setting, MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. 2017;26–32.

5. Di Carlo A. Human and economic burden of stroke. Age Ageing. 2009;38(1):4–5.

6. Bertram MY, Katzenellenbogen J, Vos T, Bradshaw D, Hofman KJ. The disability adjusted life years due to stroke in South Africa in 2008. Int J Stroke. 2013;8(100 A):76–80.

7. Teasell RW. Long-Term Sequelae of Stroke: How should you handle stroke complications? Can Fam Physician [Internet]. 1992;38:381–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2145419&tool=pmcentrez&rendertype=abstract

8. Magnani JW, Rienstra M, Lin H, Sinner MF, Lubitz S a, Mcmanus DD, et al. Atrial fibrillation: Current knowledge and future directions in epidemiology and genomics. Circulation. 2011;124(18):1982–93.

9. Huisman M V., Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 2017;69(7):777–85.

10. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11(11):639–54.

11. Reiffel JA. Atrial Fibrillation and Stroke: Epidemiology. Am J Med [Internet]. 2014;127(4):e15–6.

12. Fan X, Zhang S. The Optimal Treatment For Atrial Fibrillation In Less Developed Countries. JAFIB J Atr Fibrillation [Internet]. 2014;7(3). Available from: http://www.jafib.com/published/webFormat/Shu_Zhang/shu_zhang.pdf

13. Mensah GA, Roth GA, Sampson UK, Moran AE, Feigin VL, Forouzanfar MH, Naghavi M, Murray CJ, . Mortality from cardiovascular diseases in sub-Saharan Africa, 1990-2013: A systematic analysis of data from the Global Burden of Disease Study 2013 [Internet]. Vol. 26, Cardiovascular Journal of Africa. 2015. p. S6–10. A

14. Stambler BS, Ngunga LM. Atrial fibrillation in sub-saharan Africa: Epidemiology, unmet needs, and treatment options. Int J Gen Med. 2015;8:231–42.

Addendum 4: HREC Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Groote Schuur Hospital
Observatory 7925
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23 November 2018

HREC REF: 790/2018

Dr C Hendrikse
Division of Emergency Medicine
F-51
OMB

Dear Dr Hendrikse

PROJECT TITLE: THE PREVALENCE OF ATRIAL FIBRILLATION IN PATIENTS WITH ISCHAEMIC STROKE IN A DISTRICT HOSPITAL IN THE WESTERN CAPE (MMed-candidate-Dr M Mayet)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Mohammed Mayet will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.