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Évaluation du traitement de l'AVC aigu, de l'hypertension et de la prescription de médicaments après le congé chez les patients libanais atteints d'AVC ischémique: résultats d'une étude transversale

Diana Malaeb

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UNIVERSITE PARIS-EST CRETEIL VAL DE MARNE

ÉCOLE DOCTORALE Sciences de la Vie et de la Santé

THESE PRESENTEE

POUR OBTENIR LE GRADE DE

DOCTEUR DE

PATHOLOGIE ET RECHERCHE CLINIQUE

Par Diana MALAEB

Assessment of acute stroke treatment, hypertension, and post discharge medication prescription among Lebanese patients with ischemic stroke: Results of a cross-sectional study

Sous la direction de: Pr. Hassan HOSSEINI/Pr. Pascale SALAMEH

Soutenue le May 24, 2021

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Résumé

L'AVC ischémique aigu est une cause majeure de mortalité et de handicap et demeure un problème majeur de santé mondiale. Le respect des recommandations internationales est essentiel lors de la prise en charge d'un AVC ischémique pendant la phase aiguë afin de prévenir les complications précoces et les récurrences. Cette étude est la première au Liban à évaluer le respect des directives dans la prise en charge aiguë et post AVC ischémique et à évaluer son impact sur la mortalité hospitalière. Quant à l'évaluation des divers médicaments prescrits après l'hospitalisation, tels que les anti-thrombotiques, les antihypertenseurs, les hypolipémiants, et la mesure de la pression artérielle à différents moments à l'hôpital a été effectuée à l'aide d'une feuille de collecte de données.

Les résultats de cette étude ont mis en évidence que les recommandations internationales étaient peu respectées, ce qui explique les taux de mortalité élevés chez les patients victimes d'AVC au Liban. Nos résultats ont montré que la majorité des patients prenaient des antihypertenseurs non recommandés par les directives comme le Labétalol ou la Nicardipine. Le Labétalol était réservé aux patients présentant une tension artérielle moyenne initiale de 205/104 mm Hg tandis que d'autres agents étaient administrés à une tension artérielle initiale inférieure comprise entre 175 et 140/93 et 85 mm Hg. Il faut dire que la majorité n'a pas eu d'hospitalisation en Stroke Unit, pas de thrombolyse ni thrombectomie; faute de structure et de disponibilité de ces traitements au Liban.

Assessment of acute stroke treatment, hypertension, and post discharge medication prescription among Lebanese patients with ischemic stroke: Results of a cross-sectional study

Abstract:

Objectives: Stroke, the most common neurologic disorder and the major cause of disability and death after heart disease causing 11.8% of the total deaths worldwide, is defined as a rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 hour. This study aims to assess appropriateness of hypertension treatment in acute stroke and its adherence with the choice of medications tailored according to blood pressure readings and investigate the degree of physician adherence with the international guidelines for post-stroke discharge medications among Lebanese hospitals.

Patients and Methods: This was a pilot study performed in three Lebanese hospitals where medical records of ischemic stroke patients were used to collect required data. The study enrolled ischemic stroke patients older than 18 years of age, admitted to intensive care unit or internal medicine department. Patients with hemorrhagic stroke were excluded. Statistical analysis was done using IBM Statistical Package for the Social Science software. The significance level is $p\text{-value} \leq 0.05$.

Results: Out of 200 patients with stroke, 64.7 % were males. The difference of systolic blood pressure (SBP) from baseline, 2 hour, and after 24 hour showed significant decrease by mean value 25.18 ± 33.45 ($P < 0.001$), and 6.44 ± 22.11 ($P = 0.019$) respectively. Also, diastolic blood pressure (DBP) showed significant decrease between baseline and after 24 hour by a mean value 12.17 ± 13.63 ($P \text{ value} < 0.001$). Labetalol and amlodipine were administered to patients with significantly higher baseline blood pressure ($p < 0.001$). Change in SBP from baseline after 2 hour of drug administration was significantly higher with labetalol ($p = 0.028$ for patients eligible for reperfusion), amlodipine ($p = 0.014$), and nitroglycerine ($p = 0.044$). As for the change in SBP after 24 hour, it was significantly higher with labetalol just for patients not eligible for reperfusion ($p < 0.001$), and amlodipine ($p = 0.006$). As for the change in DBP, it was significantly lower after 24 hour on labetalol administration for patients not eligible for reperfusion ($p < 0.001$) and it was also lower 2 hour after administration of ramipril ($p = 0.001$) and 24 h ($p = 0.021$). Concerning post discharge medications adherence, antithrombotic drugs showed the highest percentage (73 %) followed by antihypertensive and lipid lowering agents by comparable results (47.5 % and 40.7 % respectively). The physician adherence for the three medications together showed (30.4 %).

Conclusion: Secondary prevention for critical diseases such as stroke appears to be inadequate in the study area. This study reveals the gap between American Stroke Association guideline recommendations and the clinical practice and states the impact of such a difference on patients' health.

Mots clés: AVC ischémique, Hypertension, Prise en charge, Suivi, Observance

Keywords: Acute Ischemic stroke, Hypertension, Management, Post discharge, Adherence

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Résumé

Objectifs: L'accident vasculaire cérébral, le trouble neurologique le plus courant et la principale cause de handicap et de décès après la maladie cardiaque, causant 11,8 % du total des décès dans le monde, est défini comme un signe clinique en développement rapide de perturbation focale de la fonction cérébrale durant plus de 24 heures. Cette étude vise à évaluer la pertinence du traitement de l'hypertension en cas d'AVC aigu et d'étudier le degré d'adhésion des médecins aux directives internationales sur les médicaments de sortie après un AVC dans les hôpitaux libanais.

Patients et Méthodes: Il s'agissait d'une étude pilote réalisée dans des hôpitaux libanais où les dossiers médicaux des patients victimes d'un AVC ischémique ont été utilisés pour recueillir les données requises. L'étude a recruté des patients atteints d'un AVC ischémique âgés de plus de 18 ans, admis en unité de soins intensifs ou en service de médecine. Les patients victimes d'AVC hémorragique en ont été exclus. L'analyse statistique a été effectuée à l'aide du logiciel IBM Statistical Package pour le logiciel de sciences sociales. Le niveau de signification est la valeur $p \leq 0,05$.

Résultats: Sur 200 patients victimes d'AVC, 64,7% étaient des hommes. La différence de pression artérielle systolique par rapport à la ligne de base, 2 heures et après 24 heures a montré une diminution significative de la valeur moyenne de $25,18 \pm 33,45$ ($p < 0,001$) et de $6,44 \pm 22,11$ ($p = 0,019$) respectivement. En outre, la pression artérielle diastolique a également montré une diminution significative entre la ligne de base et après 24 heures d'une valeur moyenne de $12,17 \pm 13,63$ (valeur $p < 0,001$). Le labétalol et l'amlodipine ont été administrés à des patients dont la tension artérielle initiale était significativement plus élevée ($p < 0,001$). La variation de la PAS par rapport à la valeur initiale après 2 heures d'administration du médicament était significativement plus élevée avec le labétalol ($p = 0,028$ pour les patients éligibles à la reperfusion), l'amlodipine ($p = 0,014$) et la nitroglycérine ($p = 0,044$). Quant à la variation de la PAS après 24 heures, elle était significativement plus élevée avec le labétalol uniquement pour les patients non éligibles à la reperfusion ($p < 0,001$), et de même pour l'amlodipine ($p = 0,006$). Quant à la DBP, elle a subi une forte baisse significative après 24 heures d'administration de labétalol pour les patients non éligibles à la reperfusion ($p < 0,001$) et ceci était remarquable 2 heures après l'administration de ramipril ($p = 0,001$) comme après 24 heures ($p = 0,021$). En ce qui concerne la prescription des médicaments après la sortie de l'hôpital, les médicaments anti-thrombotiques sont les plus prescrits (73%) suivis des antihypertenseurs et des hypolipidémiants (47,5% et 40,7%

respectivement). L'observance des malades pour les trois médicaments pris ensemble était de 30,4%.

Conclusion: La prévention secondaire des accidents vasculaires cérébraux semble inadéquate dans la zone d'étude. Cette étude révèle l'écart entre les recommandations internationales et la pratique clinique et indiquer l'impact sur la mortalité et la morbidité des patients.

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The PhD chapter is closed now. It is time to open a new page, with new objectives and new challenges.

Abbreviations:

AHA/ASA: American Heart Association/American Stroke Association

AIS: Acute Ischemic Stroke

BP: Blood Pressure

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

TIA: Transient Ischemic Attack

HTN: Hypertension

CBF: Cerebral Blood Flow

CPP: Cerebral Perfusion Pressure

ICP: Intracranial Pressure

MAP: Mean Arterial Pressure

AF: Atrial Fibrillation

LAA: Left Atrial Appendage

LDL: Low Density Lipoprotein

HDL: High Density Lipoprotein

NTG: Nitroglycerin

DAPT: Dual Anti-platelet Therapy

DOAC: Direct Acting Oral Anticoagulant

MI: Myocardial Infarction

Table of Contents

RÉSUMÉ	2
LIST OF TABLES	11
LIST OF FIGURES	11
ACKNOWLEDGMENTS	7
LIST OF PUBLICATIONS AND COMMUNICATIONS RESULTING FOR THE SCIENTIFIC WORK CONDUCTING IN THE FRAMEWORK OF THE PHD	12
1. INTRODUCTION	13
1.1 EPIDEMIOLOGY AND BURDEN OF STROKE.....	14
1.2 ETIOLOGY	15
1.2.1 <i>Large-Vessel Atherosclerosis</i>	16
1.2.2 <i>Cardioembolic Stroke</i>	17
1.2.3 <i>Small Vessel Disease (Lacunar Stroke)</i>	17
1.3 RISK FACTORS OF STROKE.....	18
1.3.1 <i>Non-modifiable Risk Factors</i>	18
1.3.2 <i>Modifiable Risk Factors</i>	20
1.3.3 <i>Other risk factors</i>	29
1.4 CLINICAL PRESENTATION OF ISCHEMIC STROKE	29
1.5 TREATMENT OF ISCHEMIC STROKE.....	32
1.5.1 <i>Acute Stroke Care</i>	32
1.5.2 <i>Secondary Prevention</i>	48
2. OBJECTIVES	58
3. OVERVIEW OF THE MANUSCRIPTS	58
3.1 FIRST MANUSCRIPT	58
3.1.1 <i>Introduction</i>	58
3.1.2 <i>Conclusion</i>	59
3.1.3 <i>Future research perspective</i>	59
3.2 SECOND MANUSCRIPT	60

3.2.1 Introduction	60
3.2.2 Conclusion	60
3.2.3 Future research perspective	62
3.3 THIRD MANUSCRIPT.....	62
3.3.1 Introduction	62
3.3.2 Conclusion	63
4. DISCUSSION	64
5. RESEARCH PROGRAMS	66
5.1 STRATEGIES TO ENHANCE PATIENT ADHERENCE AND EDUCATION.....	66
5.2. MEASURING AND IMPROVING PHYSICIAN ADHERENCE WITH INTERNATIONAL GUIDELINES	69
6. LIMITATIONS AND STRENGTHS	72
6.1 LIMITATIONS.....	72
6.2 STRENGTHS.....	72
6.3 CLINICAL IMPLICATIONS.....	73
6.4 LEBANESE SITUATION.....	73
7. CONCLUSION	75
ACKNOWLEDGMENTS	75
CONFLICT OF INTEREST	76
REFERENCES	76
APPENDICES	85
APPENDIX A: ARTICLE ONE.....	86
APPENDIX B: ARTICLE TWO	104
APPENDIX C: ARTICLE THREE	110
APPENDIX D: DATA COLLECTION SHEET.....	110

LIST OF TABLES

<i>Table 1: Criteria for the use of Alteplase.....</i>	<i>36</i>
<i>Table 2. Choice of antihypertensive agents</i>	<i>43</i>

LIST OF FIGURES

<i>Figure 1: National Institute of Health Stroke Scale Neurological Assessment Flow Sheet</i>	<i>31</i>
<i>Figure 2. Framework representing the interventions to enhance patient education and ensure adherence to medications.....</i>	<i>67</i>
<i>Figure 3. Theoretical framework responsible for guidelines in-adherence</i>	<i>71</i>

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1. Diana Malaeb, Sarah Cherri, Souheil Hallit, Sylvia Saade, Hassan Hosseini, Pascale Salameh. Assessment of post discharge medication prescription among Lebanese patients with cerebral infarction: Results of a cross-sectional study. *Clinical Neurology and Neurosurgery* 191 (2020) 105674.
2. Hiba Al Harfany, Lara Haidar, Sarah Cherri, Diana Malaeb, Pascale Salameh, Hassan Hosseini. Assessment of acute treatment of hypertension in ischemic stroke patients. *Clinical Neurology and Neurosurgery* 195 (2020) 105949.
3. Diana Malaeb, Sarah Cherri, Iqbal Fahs, Hala Sacre, Emane Abdallah, Pascale Salameh, Hassan Hosseini. Management of acute stroke among Lebanese patients: Assessing adherence to international guidelines. Submitted under revision.

Conference Posters:

1. Diana Malaeb, Pascale Salameh, Hassan Hosseini. Effect of sociodemographic factors on CHA2DS2 VASc score among Lebanese community patients. The 54th ASHP Midyear Clinical Meeting & Exhibition Mandalay Bay Convention Center December 8-12, 2019 Las Vegas, NV.
2. Diana Malaeb, Hassan Hosseini, Pascale Salameh. Assessment of post discharge medication prescription among stroke patients. The 54th ASHP Midyear Clinical Meeting & Exhibition Mandalay Bay Convention Center December 8-12, 2019 Las Vegas, NV.
3. Hiba Al Harfany, Nathalie Lahoud, Emilie Feghali, Lara Haidar, Diana Malaeb. Assessment of factors affecting CHA 2 DS 2 VASc score in acute stroke settings and its relation with MRS. The 54th ASHP Midyear Clinical Meeting & Exhibition Mandalay Bay Convention Center December 8-12, 2019 Las Vegas, NV.
4. Lara Haidar, Hiba Al-Harfany, Farah El Hussein, Nathalie Lahoud, Diana Malaeb., Assessment and evaluation of hypertension treatment in acute ischemic stroke. The 54th ASHP Midyear Clinical Meeting & Exhibition Mandalay Bay Convention Center December 8-12, 2019 Las Vegas, NV.
5. Diana Malaeb. Assessment of acute treatment of hypertension in ischemic stroke patients. 11th International Conference on Stroke, Neurology and Cerebrovascular Diseases. Webinar October 19-20, 2020.

1. INTRODUCTION

Stroke is the most common neurologic disorder and a major cause of disability and death, with an overall growing incidence particularly in low to middle income countries [1]. According to the World Health Organization stroke is defined as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours and leading to death, with no apparent cause other than that of vascular origin.” Although the WHO definition is widely used, it relies heavily on clinical symptoms and is now considered outdated by the American Heart Association and American Stroke Association (AHA/ASA) due to significant advances in the ‘nature, timing, clinical recognition of stroke and its mimics, and imaging findings that require an updated definition. Thus, a new definition was proposed by AHA/ ASA [2]. The AHA/ ASA statement defined central nervous system infarction as “brain, spinal cord, or retinal cell death attributable to ischemia, based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded.” More specifically, ischemic stroke is defined as “an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.” On the other hand, if symptoms last for less than 24 hours this is defined as transient ischemic attack (TIA). This updated definition wasn’t adopted by many practitioners since it caused confusion. Therefore, the patient’s clinical status (nature and duration of deficits) must remain the basis of stroke and TIA definitions because this is what matters most and has been the main

outcome of prognostic and therapeutic studies. Further, definitions focused on the clinical deficit allow inclusion of all affected persons and reduce the risk of mis-diagnosis [3].

Stroke is classified as either ischemic or hemorrhagic, with the majority being of ischemic origin [4]. The pathophysiology of ischemic stroke involves occlusion of an intracranial or extracranial carotid blood vessels that in most cases impair blood flow and leads to infarction of brain tissue supplied by that blood vessel. The vessel occlusion can occur due to a local vessel obstruction typically caused by atherosclerotic plaque, or secondary to embolization of a clot from the heart to a brain vessel as exemplified by atrial fibrillation [5].

1.1 Epidemiology and Burden of Stroke

Worldwide, stroke is the second most common cause of mortality. In 2015, stroke deaths accounted for 11.8% of total deaths worldwide, making stroke the second leading global cause of death behind heart disease [1].

Globally, the incidence of stroke due to ischemia is 68 %, while the incidence of hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage combined) is 32 % [6]. In the United States, the proportion of all strokes due to ischemia, intracerebral hemorrhage, and subarachnoid hemorrhage is 87, 10, and 3 % respectively [4]. This shows that globally, there is a higher incidence of hemorrhagic stroke in low- and middle-income countries.

In the United States, each year, approximately 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first attacks, and 185,000 are recurrent attacks [4].

Stroke trends are not precisely established in the Arab world. However, Arab nations have a high prevalence of a variety of stroke risk factors; prevalence of physical inactivity (up to 90% among women), smoking (38% in Lebanon), obesity (40% in the Arab Gulf countries), and diabetes (20% in the Arab Gulf countries) [7].

Lebanon has a high prevalence of stroke risk factors: obesity 26%, diabetes 14%, and hypertension 36%. Moreover, stroke is assumed to be the second leading cause of death in the country. According to a study done in 2015, Lahoud et al., reported an age-adjusted prevalence of 0.5% [7]. Also, according to a global study by Krishnamurthi et al., in 1990 the incidence rate of stroke in Lebanon was 113.03 per 100,000 person-years (77.69-163.31) and the mortality rate was 44.69 per 100,000 person-years (38.02-53.16). In 2010 the incidence rates increased to 131.63 per 100,000 person-years (87.6-187.3). The mortality rate dropped to 29.28 per 100,000 person-years (22.42-35.33) [6].

1.2 Etiology

Stroke is classified as either being ischemic or hemorrhagic. Around 85 % of strokes are ischemic with the remainder being hemorrhagic [4]. Ischemic stroke is caused by occlusion of a blood vessel in the brain, leading to diminished blood flow and subsequently ischemia. Ischemic stroke is further classified according to etiology. The Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) divides ischemic strokes as follows: large-vessel atherosclerosis, cardioembolic source, small-vessel disease, other determined causes, and cryptogenic [5].

1.2.1 Large-Vessel Atherosclerosis

Large vessel atherosclerosis accounts for about 25% of ischemic stroke cases. Large artery atherosclerotic disease may involve the extracranial vessels, carotid and vertebral arteries, and less commonly the aortic arch and great vessels. The mechanism of stroke in this instance is commonly arteroembolic; an arteroembolic plaque ruptures with local thrombus formation, which then embolizes to the brain. Large artery atherosclerosis may also involve the intracranial arteries and the mechanism of stroke may be in situ thrombosis on a ruptured plaque. The common locations for atherosclerotic disease burden are at the carotid artery bifurcation, the internal carotid artery siphon, the vertebral artery origin at the subclavian artery, and the fourth segment of the vertebral artery. Diabetic patients have a greater propensity to develop intracranial atherosclerotic disease [8].

These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, due to atherosclerosis. Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on computed tomography or magnetic resonance imaging are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed [5].

1.2.2 Cardioembolic Stroke

This category includes patients with arterial occlusions presumably due to an embolus arising in the heart. Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative tendencies for embolism. High-risk sources include: mechanical prosthetic valves, atrial fibrillation, left atrial/atrial appendage thrombus, recent myocardial infarction (<4 weeks), dilated cardiomyopathy, and infective endocarditis. Medium-risk sources include: heart failure, bioprosthetic cardiac valve, lone atrial fibrillation, PFO and atrial flutter [5].

1.2.3 Small Vessel Disease (Lacunar Stroke)

Lacunar stroke or small vessel disease involves the small penetrating arteries, and accounts for 25% of all ischemic strokes. Lacunar strokes are small (0.2 to 15 mm in diameter) subcortical strokes. Lacunes are commonly located in the basal ganglia, internal capsule, thalamus, or brain stem. Despite the fact that lacunar strokes are relatively small, they cause severe neurological deficits because of their strategic location. Two pathological types of small-artery disease are responsible for most lacunes: 1) lipohyalinosis, characterized by segmental disorganization of the vessel wall with replacement by fibrin and collagen deposits, and 2) microatheroma in which a small atheromatous plaque occludes the origin of the affected penetrating vessel, which tends to result in larger lesions. Microatheroma is believed to be responsible for larger subcortical infarcts, whereas lipohyalinosis tends to affect smaller arteries leading to smaller subcortical infarcts [9] [10]. Classic syndromes arise because of lesion location: (1) pure motor stroke; (2) pure sensory stroke; (3) clumsy hand–dysarthria syndrome; (4) ataxic hemiparesis; (5) sensorimotor stroke [5].

1.3 Risk factors of stroke

Since stroke is a heterogeneous disease, it has a variety of risk factors. Risk factors for stroke can be categorized as modifiable and non-modifiable. Non-modifiable risk factors for stroke include age, sex, race-ethnicity, and genetics. While, the modifiable risk factors of stroke are hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, obesity, alcohol or drug abuse, and oral contraceptive use [11]. The modifiable risk factors are of utmost importance, because preventative strategies are aimed at reducing these factors and subsequently reducing the risk of stroke.

1.3.1 Non-modifiable Risk Factors

1.3.1.1 Age

In general, stroke is a disease of aging with most strokes occurring in people older than 65 years of age [4]. Aging is the strongest non-modifiable risk factor for ischemic stroke, and older stroke patients have higher mortality and morbidity and poorer prognosis than their young counterparts. Several aging related changes in the brain have been identified that are associated with an increase in vulnerability to ischemic stroke in the elderly. These changes include age-related alterations in cerebral blood vessels, a reduction in cerebral blood flow with age, and an increase in blood brain barrier permeability[12].

1.3.1.2 Gender

The relationship of sex to stroke risk depends on age. In early adulthood (up until age of 45), males have a higher incidence of ischemic stroke than females [4]. In middle age (ages of 45 – 54 years), the rates of ischemic stroke begin to increase in women, concomitant with the

onset of menopause and a decline of female sex hormones [13].

After middle age (55 years and older), stroke rates continue to increase in women, reaching a stroke incidence that is comparable to males. In elderly females beyond the age of 85, a higher risk of stroke is reported in females. Overall, more strokes occur in women than men, because of the longer life span of women compared with men [4]. A study performed in Europe found that the risk of stroke increased by 9% per year in men and 10% per year in women [14]. The reasons behind these findings have not been fully elucidated.

1.3.1.3 Race

There are well-documented racial disparities in stroke. Blacks are at twice the risk of incident stroke when compared with their white counterparts and have higher mortality associated with stroke. Hispanic/Latino Americans also have an increased risk of stroke in some cohorts. According to the REGARDS study (REasons for Geographic And Racial Differences in Stroke), one reason for the racial disparities could be the higher prevalence of stroke risk factors, such as hypertension, obesity, and diabetes mellitus, among blacks. However, these additional risk factors do not completely explain the increased risk seen in these racial-ethnic groups. Black race has been identified as a factor in the relationship between rurality and stroke risk, but this could be attributed to issues with access to health care [15].

1.3.2 Modifiable Risk Factors

1.3.2.1 Hypertension

Hypertension (HTN) is the most important modifiable risk factor for stroke, with a strong, direct, linear, and continuous relationship between blood pressure and stroke risk. In INTERSTROKE, hypertension was the most important stroke risk factor: using a definition of hypertension that included both a history of hypertension and a blood pressure measurement of 160/90 mm Hg, the population attributable risk, or proportion of strokes in the population attributable to hypertension, was 52%. For ischemic stroke, the population attributable risk was 45% [16].

The mechanism of stroke due to hypertension is complex and generally occurs due to longstanding hypertension. During this long period, a series of changes take place in the cardiovascular and cerebrovascular system. These changes, such as vascular remodeling, altered cerebral blood flow (CBF) auto regulation, inflammation, and oxidative stress contribute to the pathogenesis of stroke in hypertension [16].

Vascular Remodeling

Sustained elevations in blood pressure have profound effects on the structure of cerebral blood vessels. Two types of remodeling are described, inward eutrophic or inward hypertrophic remodeling, depending on whether the media cross-sectional area is enlarged. In hypertrophic remodeling, the media thickens to encroach into the lumen, resulting in increased media cross-sectional area and media/lumen ratio. The size of

vascular smooth muscle cells (VSMCs) increases and there is accumulation of extracellular matrix proteins, such as collagen and fibronectin, in the vessel wall. In eutrophic remodeling, smooth muscle cells undergo a rearrangement that leads to a reduction in the outer and inner diameters, whereas media/lumen ratio is increased and cross-sectional area is unaltered. In this case, the change in VSMCs size is negligible, and the reduction in lumen is due to a reorganization of cellular and acellular material in the vascular wall, accompanied by enhanced apoptosis in the outer regions of the blood vessel. Remodeling is damaging because it reduces the vessels' lumen and increases vascular resistance, and has emerged as a potential risk factor for cardiovascular events and cerebrovascular disease. Moreover, longstanding HTN leads to arterial stiffening by inducing the deposition of collagen and elastin fragmentation in the walls of large arteries. Arterial stiffening leads to an increased pulse pressure which is a good predictor of stroke and cognitive decline [17].

Altered Cerebral Autoregulation

Cerebral auto regulation is a homeostatic process that regulates and maintains cerebral blood flow (CBF) constant across a range of blood pressures. The original conceptualization was proposed by Lassen as a triphasic curve consisting of the lower limit, the plateau and the

upper limit. In healthy adults, the limits are between 50 and 150 mm Hg cerebral perfusion pressure (CPP) or 60 and 160 mm Hg mean arterial pressure (MAP), where $CPP = MAP - \text{intracranial pressure (ICP)}$. This homeostatic mechanism ensures that as MAP or CPP increases, resistance increases (vasoconstriction) in the small cerebral arteries. Conversely, this process maintains constant CBF by decreasing cerebrovascular resistance or vasodilation when MAP or CPP decreases [18].

Cerebral blood flow (CBF) reductions impair neuronal function and, if prolonged induce brain damage. HTN induces profound alterations of the regulatory mechanism, which, in concert with the structural changes described above, compromise the blood supply to the brain. HTN alters cerebrovascular auto regulation leading to a shift of the pressure-flow relationship to the right, such that higher pressures are needed to maintain the same level of cerebral perfusion. The lateral shift may be also associated with a reduction in resting CBF, resulting in a downward displacement of the curve. These alterations reduce cerebral perfusion at each level of blood pressure, compromising the ability of the brain to maintain adequate CBF in the face of hypotension or arterial occlusion. The mechanisms of the effects of HTN on auto regulation are not completely understood and has been shown that the self-regulation is lost during a stroke [19].

Oxidative Stress

Oxidative stress is a condition in which generation of Reactive Oxygen Species exceeds the capacity of the antioxidant defense system. There is compelling evidence that oxidative stress play a critical part in the pathogenesis of hypertension, and stroke as a long-term complication. In the cerebral circulation, angiotensin II has been implicated in reactive

oxygen species (ROS) particularly superoxide generation via activation of the enzyme NADPH oxidase. Peroxynitrite is the product of the reaction between nitric oxide and the radical superoxide. It can induce DNA damage and lipid peroxidation, change protein function. Peroxynitrite exerts deleterious effects on cerebral blood vessels, which can account for the cerebrovascular dysfunction induced by Ang II [20].

1.3.2.2 Diabetes

It is well known that diabetes causes various microvascular and macrovascular complications, one of which is stroke. Diabetes is a major risk factor for stroke and is associated with an increase in overall stroke mortality. Compared with nondiabetic patients, diabetic patients have at least twice the risk for stroke, and approximately 20% of diabetic patients will die from stroke, making it one of the leading causes of death in this population. Diabetes duration has also been shown to increase the risk of ischemic stroke disease, with every year of diabetes duration increasing the risk by 3% [21].

There is a significant association between elevated glucose levels (fasting, postprandial, and glycated hemoglobin) and the incidence of stroke, independent of other traditional cardiovascular risk factors in patients with type 2 diabetes [22].

Among diabetics numerous risk factors play a role together to promote the development of ischemic stroke. These risk factors can be classified as diabetes-specific factors such as hyperglycemia and vascular risk factors such as hypertension and dyslipidemia. In addition to these also genetic, demographic, and lifestyle factors contribute in varying degrees to the overall risk of the subjects with diabetes mellitus [21].

Hyperglycemia contributes to the pathogenesis of stroke through several possible pathways. The possible pathways include: increased polyol pathway flux, increased advanced glycation end product formation, activation of protein kinase C isoforms, and increased hexosamine pathway flux [23].

These pathogenic pathways lead to the generation of reactive oxygen species which may lead to endothelial dysfunction by reducing the bioavailability of endothelium-derived nitric oxide (NO). The formation of Advanced Glycosylation End Products accelerates the atherosclerotic process by promoting low-density lipoprotein (LDL) uptake and oxidation leading to foam cell formation. These complex changes lead to the typical diabetic milieu that is characterized by a chronic state of low-grade inflammation, endothelial dysfunction, hypercoagulability, dyslipidemia and insulin resistance. Moreover, there is a higher prevalence and incidence of cardiometabolic risk factors such as obesity, hypertension, and dyslipidemia in patients with diabetes that add on to stroke risk [23].

There are clear differences in stroke patterns between patients with diabetes and those without diabetes. Patients with diabetes have a higher proportion of ischemic stroke compared to hemorrhagic strokes. Also, lacunar stroke is the most common stroke type. This may be due to the higher prevalence of microvascular disease and the co-existence of hypertension seen in this patient group [22].

1.3.2.3 Atrial Fibrillation (AF)

The most disabling consequence of atrial fibrillation (AF) is ischemic stroke. In the setting of AF, a thrombus originating from the heart travels to the brain's vascular system resulting in the occlusion of a brain blood vessel and damage to the brain tissue. As described

above, this is known as a cardioembolic stroke. The mechanism of thrombus formation in AF is a multifactorial process that includes changes in flow, atrial anatomy, prothrombotic alterations in blood constituents, and inflammation[24].

The failure of fibrillating atria to contract results in an increase in atrial pressure, atrial stretch, and dilation which lead to blood stasis. Also, the erratic atrial wall motion and abnormal blood flow lead to injury of the endothelium of the fibrillating atria, thus leading to activation of the clotting cascade with platelet adhesion and aggregation. Activated platelets provide a catalytic surface for assembling plasma factors of the prothrombinase complex and subsequent thrombin formation, fibrin generation, and thus thrombus consolidation.

Attached to each atrium is an appendage. The left atrium and particularly the left atrial appendage (LAA) is the source of cardioembolic emboli in most cases of AF. As noted by Blackshear and Odell who identified that the LAA is the source of up to 90% of left atrial thrombi in nonvalvular AF and 57% in valvular AF [25].

This is due to the morphology of the LAA, a frequently long, narrow, and hooked extension of the left atrium which creates an anatomic environment for blood stasis and thrombus formation.

It was previously thought that blood stasis was the sole mechanism of stroke in AF, however recent evidence also indicates that patients with AF are in a hypercoagulable state. Platelet activation is enhanced in patients with AF as determined by increased plasma levels of platelet derived b-thromboglobulin and platelet factor. In addition, in patients with AF, elevated levels of coagulation parameters such as thrombin-antithrombin III complex, D-

dimers, fibrinogen, prothrombin fragments 1 and 2, and von Willebrand factor (vWF) have been described, indicating a hypercoagulable state[26].

1.3.2.4 Dyslipidemia

The relationship between lipids and stroke is complex. In most, but not all, observational studies, there is an association between higher total and LDL cholesterol levels and increased ischemic stroke risk [27].

The reason for these differences between studies could be explained by the differential association with ischemic stroke subtypes. The strongest association is between lipids and large artery atherosclerosis, while dyslipidemia is less likely to play a major role in the pathogenesis of other ischemic stroke subtypes. In a case-control study, the association between cholesterol and ischemic stroke risk was strongest for large artery atherosclerosis (OR=3.2) [28].

The association between dyslipidemia and large artery atherosclerotic stroke subtype was also shown in two other Japanese studies [29, 30].

There is strong evidence that LDL, along with other factors, play a fundamental role in the development of atherosclerosis. Atherosclerotic lesions or plaques may protrude into the lumen of the arteries, causing occlusion thus limiting blood flow. These plaques can rupture leading to thrombosis, thus completely blocking blood flow. These processes usually occur in the large intracranial and extracranial cerebral blood vessels therefore, leading to ischemic stroke [29].

1.3.2.5 Cigarette smoking

Cigarette smoking is an independent predictor of cerebrovascular disease in both men and women. Smokers have a relative risk of ischemic stroke of 1.92 times higher as compared to non-smokers. Cigarette smoking increases heart rate, blood pressure, the risk of thrombus formation, and the development of atherosclerosis. Also, smoking increases blood viscosity, fibrinogen and platelet aggregation, and decreases high density lipoprotein (HDL) cholesterol [31]. In addition, according to a study conducted by Al Hajje et al., waterpipe and cigarette smoking were observed to have a stronger association with stroke in current smokers than non-smokers among Lebanese population [32].

1.3.2.6 Physical inactivity

It is well documented that physical activity exerts a beneficial protective effect on reduction of stroke risk and recurrence throughout life including in older adults. In the Nurses' Health Study and the Women's Health Initiative, mild exercise such as walking was associated with reduced risk, and in postmenopausal women, slow walking speed was a strong independent predictor of increased risk of stroke. In a longitudinal study of older, multiethnic, urban-dwelling stroke free individuals, greater exercise intensity was found to be associated with lowering stroke risk for men. A meta-analysis report of physical activity and stroke risk concluded that moderately and highly active adults had a lower risk of stroke than low-activity adults. Moderately active adults had a 20% stroke risk reduction and in highly active adults, a 27% risk reduction[33].

Possible mechanisms activated in physical activity to reduce risk include reduction in plasma fibrinogen, decrease aggregability of platelets, lowering blood pressure and reducing weight. Despite the documented benefits of an active life as demonstrated in a number of longitudinal studies, sedentary lifestyles continue to be an increasing trend. For stroke, the benefits of even light to moderate activities results in an important health benefits in the pathway to stroke reduction [33].

1.3.2.7 Alcohol Consumption

The association between alcohol intake and stroke morbidity and mortality is J-shaped. Light and moderate alcohol consumption is associated with reduced risk of stroke, while heavy alcohol consumption is associated with an increased risk [34].

Heavy alcohol use likely increases the risk of stroke by increasing the risk of hypertension, atrial fibrillation, cardiomyopathy, and diabetes[35-37].

A recent systematic review and meta-analysis included 27 prospective studies with data on ischemic stroke (25 studies), intracerebral hemorrhage (11 studies), and/or subarachnoid hemorrhage (11 studies) published through September 1, 2016. Light and moderate alcohol consumption was associated with a lower risk of ischemic stroke, whereas high and heavy drinking was associated with an increased risk; the overall RRs were 0.90 (95% CI, 0.85–0.95) for < 1 drink/day, 0.92 (95% CI, 0.87–0.97) for 1 to 2 drinks/day, 1.08 (95% CI, 1.01–1.15) for > 2 to 4 drinks/day, and 1.14 (95% CI, 1.02–1.28) for > 4 drinks/day [38].

1.3.3 Other risk factors

Several other risk factors of stroke have been proposed but are considered to play an inferior role. Some of these risk factors include oral contraceptive use, inflammatory processes, migraine, sleep apnea syndrome, prothrombin activator inhibitor complex deficiency, hypotension, high C-reactive protein, certain infections *as* Chlamydia pneumoniae, Helicobacter pylori, Legionella pneumophila, chronic bronchitis, periodontal disease, and hyperuricemia [39-42].

1.4 Clinical presentation of ischemic stroke

Clinical presentation of stroke depends on the area of the brain affected by occlusion of the arteries. AHA/ASA have popularized the FAST algorithm to diagnose stroke in the prehospital setting. FAST acronym stands for facial droop, arm weakness, slurred speech and time of onset. Another easy way to remember to signs of stroke is the 6S method [43].

Stroke: 6S Method to Diagnose Stroke

1. **Sudden** (symptoms usually start suddenly)
2. **Slurred Speech** (speech is not clear, as if drunk)
3. **Side Weak** (face, arm or leg or all three can get weak)
4. **Spinning** (vertigo)
5. **Severe headache**
6. **Seconds** (note the time when the symptoms start and rush to the hospital)

Befast: **B**alance (loss of balance/dizziness), **E**yes (disturbance of vision in one or both eyes), **F**ace (facial droop), **A**rm (weakness)and **S**peech (slurred) test.

All the symptoms need not be present to diagnose stroke. Any of the above-mentioned symptoms can be present and is helpful in diagnosing ischemic as well as hemorrhagic stroke. For complete assessment of a stroke patient it is recommended to use the NIH stroke scale (NIHSS) as illustrated in Figure 1.

Figure 1: National Institute of Health Stroke Scale Neurological Assessment Flow Sheet [43]

To be completed by physician			DATE: TIME:	DATE: TIME:
Category	Description/ Score UN= Untestable	Scoring Key	SCORE ▼▼▼	SCORE ▼▼▼
1a. Level of Consciousness (Alert, drowsy, etc.)	Alert Drowsy Stuporous Coma	0 1 2 3		
1b. Level of Consciousness Questions (Month, age)	Answers both correctly Answers one correctly Incorrect	0 1 2		
1c. Level of Consciousness Commands (Open/close eyes, squeeze and let go)	Obeys both correctly Obeys one correctly Incorrect	0 1 2		
2. Best Gaze (Eyes open - patient follow examiners finger / face)	Normal Partial gaze palsy Forced Deviation	0 1 2		
3. Visual (Introduce visual stimulus, or threat to patient's visual field quadrants)	No visual loss Partial hemianopia Complete hemianopia Bilateral hemianopia	0 1 2 3		
4. Facial Palsy (Show teeth, raise eyebrows and squeeze eyes shut)	Normal Minor Partial Complete	0 1 2 3		
5. Motor, Arm: Left / Right	No drift Drift Can't resist gravity No effort against gravity No movement Amputation, joint fusion (explain)	Left / Right 0 / 0 1 / 1 2 / 2 3 / 3 4 / 4 UN / UN		
6. Motor, Leg: Left / Right	No drift Drift Can't resist gravity No effort against gravity No movement Amputation, joint fusion (explain)	Left / Right 0 / 0 1 / 1 2 / 2 3 / 3 4 / 4 UN / UN		
7. Limb Ataxia (Finger-nose, heel down shin)	Absent Present in one limb Several limbs Amputation, joint fusion (explain)	0 1 2 UN		
8. Sensory (Pin prick to face, arm [trunk] and leg—compare side to side)	Normal Partial Loss Severe Loss	0 1 2		
9. Best Language	No aphasia Mild to moderate aphasia Severe aphasia Mute	0 1 2 3		
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	Normal articulation Mild to mod. dysarthria Near to unintelligible or worse Intubated or other physical barrier	0 1 2 UN		
11. Extinction or inattention (Use information from prior testing to identify neglect or double simultaneous stimuli)	No neglect Partial neglect Complete neglect	0 1 2		
		Total Score →		
Place in the order section of patient's chart		MD Signature →		

 NIH STROKE SCALE NEUROLOGICAL ASSESSMENT FLOW SHEET	APPLY PATIENT LABEL HERE Approved: _____ Original – Medical Record
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1.5 Treatment of Ischemic Stroke

The goal of therapy in acute ischemic stroke is to preserve and maintain tissue perfusion to avoid infarction. Therapy should be targeted to restore blood flow to the compromised regions and improve collateral flow. Restoring blood flow can minimize the effects of ischemia only if performed quickly. The treatment of ischemic stroke is divided into acute stroke care and secondary prevention [44]. In the acute phase, treatment is aimed at reperfusion of the ischemic tissue with IV thrombolytic or mechanical thrombectomy, management of blood pressure, and avoiding complications. After the acute phase, treatment is aimed at reducing the risk of recurrent stroke by determining the most likely etiology and directing treatment towards the cause(s).

1.5.1 Acute Stroke Care

The main goals of treatment in the acute phase of ischemic stroke are: acute reperfusion and management of blood pressure.

1.5.1.1 Acute Reperfusion

For acute reperfusion two strategies are available: IV thrombolytics and mechanical thrombectomy. Mechanical thrombectomy should be considered in all patients, even if fibrinolytic therapy is administered. The AHA/ASA guidelines do not recommend observation for a clinical response after IV alteplase administration even if mechanical thrombectomy is considered a treatment option [4].

Endovascular thrombectomy in the first six hours is much better than standard medical care in patients with large vessel occlusion in the arteries of the proximal anterior circulation[44].

In acute stroke, ischemia is rarely complete at presentation. During acute ischemic stroke (AIS) there are two regions of ischemia the core and the penumbra. The core, where the blood clot occurs, receives roughly 10% to 25% of normal blood flow, leading to infarction and tissue necrosis [45].

The penumbra, which is the ischemic tissue surrounding the core, can receive blood from collateral circulation, delaying completion of the infarct. These neurons are salvageable if reperfused in time. Thrombolysis with IV alteplase can lyse the clot and restore blood flow to the ischemic penumbra. IV alteplase is the only FDA approved treatment for patients with AIS [44]. Alteplase is a recombinant tissue-type plasminogen activator (rt-PA). The advent of alteplase has dramatically revolutionized the treatment of AIS since it improves patients' outcomes and resolves their neurologic deficits [46]. Despite its benefits, alteplase use is not without risks. The most feared side effect of alteplase is symptomatic intracerebral hemorrhage (sICH). To reduce the rate of this side effect, patients with AIS are carefully selected and a strict eligibility criterion is in place. Table 1 lists the inclusion/ exclusion criteria.

Its FDA approval was based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trials which showed that IV rt-PA administration within 3 hours of ischemic stroke symptoms onset improved clinical outcomes compared to placebo

[47]. An alteplase dose of 0.9 mg/kg was used in the NINDS trial. And the total dose of alteplase is divided into a 10% bolus and 90% as an infusion over 60 minutes [47][48].

While FDA labeling still indicates that patients eligible for IV rt-PA should be treated within 3 hours, the AHA/ASA treatment guidelines recommend that IV rt-PA also be administered to eligible patients 3 to 4.5 hours after stroke, based on results of the European Cooperative Acute Stroke Study III (ECASS III) trial. In 2008 the ECASS III trial studied IV rt-PA versus placebo in the 3 to 4.5 hour time window from onset of stroke symptoms. This trial also showed benefit of IV tPA in functional outcomes. However, the rate of symptomatic intracerebral hemorrhage was significantly higher in the IV rt-PA group, but no difference in mortality rate was observed. Therefore, IV rt-PA is considered safe in this extended time window [49].

Although IV alteplase may be administered up to 4.5 hours after stroke onset, several trials have shown that earlier administration correlates with better outcomes[50].

“Time is brain” during AIS and timely reperfusion is of utmost importance. Nearly 2 to 10 million neurons are lost during each minute of untreated stroke [51].

Thus, shorter door-to-needle times of IV rt-PA administration can save more neurons and improve functional outcomes. A meta-analysis of several studies supports this conclusion[52].

Based on this, the AHA/ASA recommend a door-to-needle time of < 60 minutes for IV rt-PA administration once the patient arrives at the hospital [50].

Despite the clear data that support its timely use, utilization of IV rt-PA remains significantly low in both developed and developing countries [53]. The utilization of thrombolytic therapy for acute stroke patients in the developing countries is low (less than 1% to 3%) compared to developed countries (up to 10%) [54]. In Lebanon, the results showed that around 10.3% of the acute ischemic stroke patients who met the eligible criteria received rt-PA administration [53].

Results from Get with the Guidelines Stroke program revealed that only 7% of all stroke patients arrived within a time period eligible for IV rt-PA, and only 77% of patients eligible for rt-PA were given rt-PA within 2 hours of symptom onset [55].

Table 1: Criteria for the use of Alteplase [4]

Inclusion Criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Treatment within 4.5 hours
Age ≥18 years
Exclusion Criteria
Current intracranial hemorrhage
Subarachnoid hemorrhage
Ischemic stroke within 3 months
Severe head trauma within 3 months
History of intracranial hemorrhage
Coagulopathy (platelet count <100,000, activated partial thromboplastin time (aPTT) >40 second, or prothrombin time (PT) >15 second)
Active internal bleeding
Intracranial/intraspinal surgery within 3 months
Intra-axial intracranial neoplasm
Current severe uncontrolled hypertension (systolic ≥185 mmHg or diastolic ≥110 mmHg)
Gastrointestinal malignancy or gastrointestinal bleed within 21 days
Therapeutic doses of low molecular weight heparin received within 24 hours (eg, to treat venous thromboembolism and acute coronary syndrome); this exclusion does not apply to prophylactic doses
Current use of a direct thrombin inhibitor or direct factor Xa inhibitor with evidence of anticoagulant effect by laboratory tests such as aPTT, international normalized ratio (INR), or appropriate factor Xa activity assays
Additional exclusion criteria Between 3 and 4.5 hours:
Age >80 years
Oral anticoagulant use regardless of INR
Severe stroke (national institute of health stroke scale (NIHSS) score >25)
Combination of both previous ischemic stroke and diabetes mellitus

IV alteplase has numerous limitations including a low potential to recanalize occluded vessels with a large (>8 mm) thrombus[56], resulting in a poor recanalization rate (13% to 50%) in large vessel occlusion stroke and a low rate of benefit in the patients having the most disabling strokes [57].

To overcome these limitations, alternative therapies have been studied. Tenecteplase is one of these alternative therapies.

Tenecteplase (TNK) is a genetically engineered variant of rt-PA that has a longer half-life and is more fibrin specific than rt-PA. TNK has properties which make it a faster and more complete thrombolytic agent and, at the same time, with less bleeding complications and early reocclusions [58].

Furthermore, TNK can be given as a one-time bolus without need for an infusion[59].

In the Tenecteplase versus Alteplase for Acute Ischemic Stroke (TAAIS) trial, 75 patients, who arrived <6 hour after the onset of ischemic stroke, were randomly assigned to receive either rt-PA (0.9 mg/kg) or TNK (0.1 mg/kg or 0.25 mg/kg). Patients treated with TNK had greater reperfusion rates and better clinical outcomes at 24 hour than rt-PA patients, while no significant differences in intracranial bleeding or other serious adverse events were noted between the groups. Although TNK has shown promising results, IV rt-PA is still recommended as the standard of care.

1.5.1.2 Blood Pressure Management in Acute Ischemic Stroke

Abnormal Blood Pressure

Most patients with acute ischemic stroke present with elevated blood pressure. This has been shown in two large studies: the Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST). The CAST trial enrolled 21,106 patients and from those 75% had hypertension (defined as SBP greater than 140 mmHg) within the first two days of the acute stroke [60].

Another study, the IST trial recruited 19,435 patients and reported an incidence of hypertension of 80% [61].

It is unclear whether this rise in BP is a protective mechanism to increase perfusion to the ischemic area or whether it's due to chronic hypertension or other pathological mechanisms. Under normal physiological conditions, cerebral autoregulation maintains adequate and stable cerebral blood flow despite fluctuations in mean arterial pressure (MAP). This is achieved by the small arteries and arterioles of the cerebral vasculature which constrict or dilate in response to changes in the systemic blood pressure. However, in patients with AIS cerebral autoregulation may be impaired[62].

Blood Pressure as a Prognostic Factor in AIS

Results of several observational studies have revealed a U-shaped relationship between blood pressure and poor outcomes. Both very high and very low baseline blood pressures were associated with poor outcomes. The results of an analysis from the IST which evaluated more than 17,000 patients with ischemic stroke revealed that early death increased by 17.9% for every 10 mm Hg below 150 mm Hg ($P<0.0001$) and by 3.8% for every 10 mm

Hg above 150 mm Hg ($P=0.016$). Moreover, the rate of recurrent ischemic stroke within 14 days increased by 4.2% for every 10mm Hg increase in SBP ($P=0.023$). Low SBP was associated with a severe clinical stroke (total anterior circulation syndrome) and an excess of deaths from coronary heart disease ($P=0.002$)[63].

Should high BP be treated?

Several studies have shown that BP declines within the first several hours to days following ischemic stroke without administration of antihypertensives [64, 65].

One of the most controversial questions that remain unanswered is whether high blood pressure in the setting of acute ischemic stroke should be treated. The rationale for lowering BP is to reduce or prevent cerebral edema and limit hemorrhagic transformation of the infarct. However, lowering BP too much in AIS worsens hypoperfusion and leads to the expansion of the ischemic core.

When to treat high blood pressure?

Treatment of the rise in blood pressure in the acute phase of ischemic stroke depends on whether the patient is eligible for acute reperfusion or not. The treatment of hypertension for patients ineligible for thrombolysis is controversial, and no strict blood pressure goals are recommended. Current AHA/ASA guidelines state that, in patients with BP < 220/120 mmHg who did not receive IV rt-PA or undergo mechanic thrombectomy and have no comorbid condition requiring antihypertensive treatment (for example, aortic dissection, acute coronary event, or acute heart failure), treatment of hypertension within the first 48 to 72 hours is not considered effective to prevent death or dependency [66].

Furthermore, multiple trials have shown that treating hypertension in the acute phase of ischemic stroke does not improve outcomes. The Scandinavian Candesartan Acute Stroke Trial (SCAST) [67] published in 2011 examined lowering blood pressure with candesartan in patients with acute ischemic and hemorrhagic stroke (approximately 85% ischemic, 15% hemorrhagic) (within 30 hours of symptom onset) and high blood pressure (defined as SBP of 140 mmHg or higher). 2029 patients were randomly allocated (1:1) to candesartan or placebo. During the 7-day treatment period, blood pressures were significantly lower in patients allocated candesartan than in those on placebo (mean 147/82 mm Hg in the candesartan group on day 7 vs 152/84 mm Hg in the placebo group; $p < 0.0001$). During 6 months' follow-up, the risk of the composite vascular endpoint did not differ between treatment groups (candesartan, 120 events, vs placebo, 111 events; adjusted hazard ratio 1.09, 95% CI 0.84–1.41; $p = 0.52$). Analysis of functional outcome (measured by the modified Rankin scale) suggested a higher risk of poor outcome in the candesartan group (adjusted common odds ratio 1.17, 95% CI 1.00–1.38; $p = 0.048$ [not significant at $p \leq 0.025$ level]). This demonstrates that there is no benefit for blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan in patients with acute stroke and raised blood pressure. Not only is it non-beneficial but the evidence suggests a harmful effect.

The most recent and largest trial to date the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) examined the effects of BP reduction[68].

The CATIS trial randomized 4071 patients with non-thrombolysed ischemic stroke within 48 hours of onset and elevated systolic blood pressure. Patients ($n = 2038$) were randomly assigned to receive antihypertensive treatment (aimed at lowering systolic blood pressure by

10% to 25% within the first 24 hours after randomization, achieving blood pressure less than 140/90 mmHg within 7 days, and maintaining this level during hospitalization) or to discontinue all antihypertensive medications (control) during hospitalization (n = 2033). The anti-hypertensive medications used were intravenous angiotensin-converting enzyme inhibitors (Enalapril, first-line), calcium channel blockers (second-line), and diuretics (third-line) either individually or in combination to achieve the targeted blood pressure reduction.

The primary outcome was a combination of death and major disability (modified Rankin Scale score ≥ 3) at 14 days or hospital discharge.

Mean systolic blood pressure was reduced from 166.7 mmHg to 144.7 mmHg (-12.7%) within 24 hours in the antihypertensive treatment group and from 165.6 mmHg to 152.9 mmHg (-7.2%) in the control group within 24 hours after randomization (difference, -5.5% [95% CI, -4.9 to -6.1%]; absolute difference, -9.1 mmHg [95% CI, -10.2 to -8.1]; $P < .001$). Mean systolic blood pressure was 137.3 mmHg in the antihypertensive treatment group and 146.5 mmHg in the control group at day 7 after randomization (difference, -9.3 mmHg [95% CI, -10.1 to -8.4]; $P < .001$). The primary outcome did not differ between treatment groups (683 events [antihypertensive treatment] vs 681 events [control]; odds ratio, 1.00 [95% CI, 0.88 to 1.14]; $P = .98$) at 14 days or hospital discharge. The secondary composite outcome of death and major disability at 3-month post treatment follow-up did not differ between treatment groups (500 events [antihypertensive treatment] vs 502 events [control]; odds ratio, 0.99 [95% CI, 0.86 to 1.15]; $P = 0.93$) [68].

Despite the controversy concerning BP management in patients with AIS ineligible for thrombolysis, BP lowering is clearly recommended above certain thresholds for patients with AIS who are eligible to receive thrombolytic therapy. For patients with ischemic stroke eligible for thrombolytic therapy, a BP >185/110 mmHg should be treated to reduce the risk of hemorrhagic transformation. Blood pressure should be lowered to below 185 / 110 mmHg prior to rt-PA therapy and maintained below 180/105 for the next 24 hours. These cut off values come from a pilot study which evaluated the factors associated with ICH formation following the use of thrombolytic therapy. This study found that an increased risk of ICH was associated with elevated diastolic BP. Therefore, in the NINDS study, a strict BP of less than 185/110 mm Hg was required for enrollment into the study and tight BP control was maintained for 24 hours with a BP goal of less than 180/105 mm Hg [61].

To further corroborate the fact that higher BP is associated with worse outcomes in patients who receive IV alteplase, Ahmed *et al.* published results from the Safe Implementation of Thrombolysis in Stroke registry. The registry included 11,080 patients and categorized patients based on their history of hypertension and whether they were treated with antihypertensives following thrombolysis. Increased SBP 2 to 24 hours after thrombolytic therapy was associated with worse outcome (symptomatic hemorrhage, mortality, functional dependence) at 3 months. The best outcomes were observed in patients with SBP values between 141 and 150 mm Hg up to 24 hours after thrombolysis [69].

Choice of Antihypertensive

In the acute phase of stroke, there is a lack of evidence to suggest a specific antihypertensive agent over the others. However, it's preferable to use agents that are

reversible, titratable and carry a low risk of increased intracranial pressure. The AHA/ASA guidelines suggest the use of IV nicardipine, labetalol, or clevidipine [66].

Table 2 provides the dosing of these agents. Intravenous nitroprusside is considered if blood pressure is not controlled on the aforementioned agents. It is considered a second line agent due to its risk of increased intracranial pressure.

Table 2. Choice of antihypertensive agents [66]

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mmHg
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or
Nicardipine 5 mg/hour IV, titrate up by 2.5 mg/hour every 5–15 min, maximum 15 mg/hour; when desired BP reached, adjust to maintain proper BP limits; or
Clevidipine 1–2 mg/hour IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/hour
Other agents (eg, hydralazine, enalaprilat) may also be considered
If BP is not maintained ≤185/110 mmHg, do not administer alteplase
Management of BP during and after alteplase or other acute reperfusion therapy to maintain BP ≤180/105 mmHg
Monitor BP every 15 min for 2 hour from the start of alteplase therapy, then every 30 min for 6 hour, and then every hour for 16 hours
If systolic BP >180–230 mmHg or diastolic BP >105–120 mmHg
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or
Nicardipine 5 mg/hour IV, titrate up to desired effect by 2.5 mg/hour every 5–15 minutes, maximum 15 mg/hour; or
Clevidipine 1–2 mg/h our IV, titrate by doubling the dose every 2–5 minutes until desired BP reached; maximum 21 mg/hour
If BP not controlled or diastolic BP >140 mmHg, consider IV sodium nitroprusside

Other Antihypertensive Agents in the Acute Setting

Nitroglycerin (NTG) is a nitric oxide donor that primarily causes venodilation, as well as arterial dilation at high doses, thereby effectively reducing preload and BP. In the ENOS (Efficacy of Nitric Oxide in Stroke) Trial, which primarily took place in Europe and Asia, the investigators studied the use of transdermal glyceryl trinitrate patch in AIS or hemorrhagic stroke patients at a dose of 5mg daily for 7 days compared to placebo. While transdermal glyceryl trinitrate was effective in lowering blood pressure, there was no significant improvement in functional outcome at 90 days[70] [71].

1.5.1.3 Treatment of Hyperthermia

Hyperthermia defined by values greater than 38 °C should be avoided and treated appropriately as increase in temperature is associated with an in-hospital mortality. Antipyretics such as acetaminophen may be used to lower temperature but induction of hypothermia is not supported [66]. Common sources of infection should be ruled out, such as pneumonia and urinary tract infections.

1.5.1.4 Treatment of Hyperglycemia

Glucose level should be maintained in the range of 140 to 180 mg/dL in the first 24 hours. Hypoglycemia defined by levels less than 60 mg/dL should be treated to achieve normoglycemia as hypoglycemia decreases the repair of the brain which can be explained by the fact that the brain is dependent on oxidative pathways that require glucose for metabolism, and the metabolic demand of the brain is high. However, hyperglycemia decreases reperfusion due to oxidation of nitric oxide-dependent mechanisms and

subsequent loss of vascular tone and is associated with an increase in mortality[72]. Hyperglycemia in the acute stroke should be treated with the rapid acting insulin to achieve the target blood glucose level [66].

1.5.1.5 Treatment of Dyslipidemia

High-intensity statins through either atorvastatin 40-80 mg daily or rosuvastatin 20-40 mg daily are recommended for patients who are 75 years old or younger and who have clinical atherosclerotic cardiovascular disease [66]. In addition, statins should be continued if the patients were already on statins prior to the ischemic stroke.

1.5.1.6 Anticoagulants

Anticoagulation therapy is not routinely indicated for acute stroke management due to the associated risk of intra or extra-cranial bleeding regardless of the benefits they provide. Controversy exists over the timing for initiation of anticoagulation, the efficacy of the treatment in relation to stroke etiology, the ideal dose of anticoagulants, and the use of novel anticoagulants [73, 74]. Current AHA/ASA 2018 guidelines provide against the use of anticoagulation in acute ischemic stroke regardless of the extent of stenosis [66] . Usually, if the size of the stroke is small to moderate, anticoagulation can be started within 7-14 days and delayed for a couple of weeks if small hemorrhagic transformation after acute stroke was documented [75, 76].

1.5.1.7 Deep Vein Thrombosis Prophylaxis

Intermittent pneumatic compression is recommended for all immobile patients unless there are contraindications. Although prophylactic heparin is often used for immobile patients, the benefit is not clear in stroke patients [77].

1.5.1.8 Dual Antiplatelet Therapy (DAPT)

Stroke is common during the first few weeks after TIA or minor ischemic stroke. The risk of another stroke occurring after a TIA or minor stroke is high, with approximately 10 to 20% of patients having a stroke within 3 months after the index event; most of these strokes occur within the first 2 days [78].

Therefore, antiplatelet therapy is indicated for patients with AIS within 24 to 48 hours after onset. And for those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later.

Results from two trials using dual antiplatelet therapy (aspirin plus clopidogrel) have shown benefit compared to aspirin alone in patients with minor stroke. The CHANCE trial was a randomized, double-blind, placebo-controlled trial conducted in China which recruited 5170 patients. These patients were assigned within 24 hours after the onset of minor ischemic stroke or high-risk TIA to combination therapy with clopidogrel and aspirin (clopidogrel at an initial maximum dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to placebo plus aspirin (75 mg per day for 90 days). Stroke occurred in 8.2% of patients in the clopidogrel–aspirin group, as compared with 11.7% of those in the aspirin group (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group ($P = 0.73$). The authors concluded that the combination of clopidogrel and aspirin is superior to aspirin

alone for reducing the risk of stroke in the first 90 days with no increase in the risk of hemorrhage [79].

The CHANCE trial was conducted on Chinese population; therefore its results cannot be generalized to the general population. Another trial, the POINT trial, tested the combination of aspirin and clopidogrel in an international population. The POINT trial enrolled 4811 patients with minor ischemic stroke or high-risk TIA. These patients were randomized to receive either clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a maximum dose of 325 mg per day) or the same range of doses of aspirin alone. Major ischemic events occurred in 121 of 2432 patients (5.0%) receiving clopidogrel plus aspirin and in 160 of 2449 patients (6.5%) receiving aspirin plus placebo (hazard ratio, 0.75; 95% confidence interval [CI], 0.59 to 0.95; $P = 0.02$), with most events occurring during the first week after the initial event. Major hemorrhage occurred in 23 patients (0.9%) receiving clopidogrel plus aspirin and in 10 patients (0.4%) receiving aspirin plus placebo (hazard ratio, 2.32; 95% CI, 1.10 to 4.87; $P = 0.02$). According to a previous study, patients with minor ischemic stroke or high-risk TIA who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin alone[80].

The AHA/ASA guidelines recommend administering dual antiplatelet therapy (aspirin plus clopidogrel) for patients presenting within 24 hours with minor stroke for a treatment duration of 21 days [66].

1.5.2 Secondary Prevention

Up to 25% of strokes are recurrent strokes. The case mortality rate after an initial stroke is 22% whereas in recurrent stroke the rate goes up to 41% [81].

Therefore, it is important to prevent recurrent stroke. As stated earlier, there are modifiable risk factors for stroke such as hypertension, diabetes mellitus, dyslipidemia, smoking, and physical inactivity. These risk factors are amenable for secondary prevention by the use of pharmacological therapy. Moreover, atrial fibrillation is a major cause of cardio-embolic stroke; therefore, the use of anticoagulants as prevention is an important strategy for this type of ischemic stroke. The following section will review the different strategies implemented to prevent ischemic stroke [81].

1.5.2.1 Antihypertensive Therapy

Hypertension is the most common modifiable risk factor for stroke. The prevalence of premorbid hypertension in patients with recent stroke is approximately 70% [78].

Hypertension increases the risk of recurrent stroke and several meta-analyses have shown that antihypertensives decrease the risk of recurrent stroke by approximately 30%. Although the evidence for using antihypertensive treatment to prevent recurrent stroke in stroke patients with elevated BP is compelling, questions remain about when precisely after an index stroke to initiate it, what specific agent to use, which BP goal to aim for, and whether the treatment approach should vary by index stroke etiology and baseline level of BP.

The AHA/ASA guidelines recommend resumption of antihypertensive therapy for previously treated, neurologically stable patients with known hypertension for prevention of

recurrent stroke. In addition, antihypertensive therapy should be initiated for previously untreated, neurologically stable patients with any type of stroke or TIA who have a blood pressure that is above target. Generally, they are started or restarted 24 to 48 hours after ischemic stroke onset and during hospitalization.

Monotherapy is recommended when blood pressure is <20/10 mmHg above goal. According to hypertension guidelines the choice of drug is as follows: for adults who experience a stroke or TIA, treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful [82].

This recommendation is based on several randomized controlled trials (RCTs) and systematic reviews [83-85]. Beta blockers have shown that they do not reduce stroke risk compared to other antihypertensives and are not recommended unless there is a compelling indication for them [86].

Despite the recommendations for choice of antihypertensives, calcium channel blockers have not shown statistical difference from angiotensin inhibitors and diuretics[87, 88].

According to hypertension guidelines a BP goal of less than 130/80 mm Hg is recommended for adult patients who have had a stroke or TIA [82].

1.5.2.2 Anticoagulant Therapy (non-Cardioembolic Stroke)

Anticoagulation is not recommended for prevention of stroke in patients with non-cardioembolic stroke based on the results of several studies comparing aspirin with warfarin. The WARSS study enrolled 2206 patients with recent (within 30 days) ischemic stroke

without evidence of cardioembolic source. It compared aspirin 325 mg with warfarin with a target INR of 1.4 to 2.8. There were no significant differences between the groups in terms of efficacy or bleeding risk [89].

Another trial, the WASID trial compared warfarin and aspirin in those with recent stroke and documented 50 to 99% intracranial stenosis (who had no evidence of significant carotid or cardio-embolic disease) and revealed no benefit from warfarin in terms of stroke recurrence which was similar in both groups (HR 1.04, 95% CI 0.73 to 1.48). However, there was an increased hemorrhage rate and increased mortality [90].

The SPIRIT trial included 1316 patients with TIA or minor stroke. The trial was terminated early due to increased bleeding, although it did involve a high target INR (3 to 4.5). The ESPRIT trial enrolled 1038 patients with recent ischemic stroke. It compared aspirin with warfarin (target INR 2 – 3). There was no difference in rate of the primary outcome between treatment groups although ischemic events were lower following warfarin (HR 0.73, 95% CI 0.52 to 1.01) but major hemorrhage rate was higher (HR 2.56, 95% CI 1.48 to 4.43) [91].

1.5.2.3 Anticoagulant Therapy (Cardioembolic Stroke)

Due to the thromboembolic risk associated with atrial fibrillation (AF), chronic oral anticoagulation is recommended for most AF patients. However, such therapy is associated with an increased risk of bleeding and recommendations for its use must take both benefit and risk into account. Scoring algorithms are now commonly employed to help predict stroke risk and identify those with atrial fibrillation most likely to benefit from anticoagulant treatment. The CHA2DS2-VASc score is available to calculate whether a patient with non-

rheumatic atrial fibrillation requires anticoagulation. This score is endorsed by the American and European guidelines [92].

The most recent update in the atrial fibrillation guidelines recommend that for men with a CHA₂DS₂-VASc score of 2 or greater and women with a CHA₂DS₂-VASc score of 3 or greater, oral anticoagulation should be administered. Options include: vitamin K antagonists such as warfarin and the direct-acting oral anticoagulants (DOACs) also known as non-vitamin K oral anticoagulants (NOACs). The NOACs include rivaroxaban, apixaban, edoxaban (direct factor Xa inhibitors) and dabigatran (direct thrombin inhibitor). Oral anticoagulants might be reasonable for men with CHA₂DS₂-VASc score of 1 and women with CHA₂DS₂-VASc score of 2 [92].

NOACs are preferred over warfarin in patients with non-valvular AF (valvular heart disease is defined as moderate-to-severe mitral stenosis or a mechanical heart valve). Warfarin remains the drug of choice in patients with valvular AF [92].

1.5.2.4 Statins

Statins are the most commonly prescribed lipid lowering therapy. Numerous trials have been published on their beneficial effects on low-density lipoprotein cholesterol (LDL-C), cardiovascular disease events, and mortality. Also, the benefits of statin treatment have been shown for primary and secondary stroke prevention. Interestingly, epidemiologic and observational studies have not shown a clear association between cholesterol levels and all causes of stroke[93].

Moreover, non-statin drugs (such as fibrates and bile acid sequestrants) have shown no significant impact on stroke incidence even though they lowered cholesterol levels. This suggests that statins have an extra non-lipid lowering mechanism by which they decrease the risk of initial and recurrent stroke. This mechanism has not been fully elucidated. However, it has been proposed that statins' pleiotropic effects play a role in stroke prevention. These effects include plaque stabilization, antithrombotic effects, reduction in inflammation, improving endothelial function and slowing carotid arterial disease progression.

The Heart Protection Study (HPS) [94] provided the first evidence of the benefit of statin therapy in secondary stroke prevention. Patients with high risk of vascular events (n=20,536) were included in the study. Simvastatin treatment significantly reduced the risk of vascular events and those events that cause strokes. This effect was also noted in patients with relatively low levels of LDL-C (<116 mg/dL). The HPS included 3280 randomly chosen stroke patients and 1822 stroke patients without established CHD. In all stroke patients, there was a 19% RRR of major vascular events, and in the stroke patients without established CHD, the reduction in the risk of major vascular events was 23%. However, the HPS did not find a reduction in stroke risk among patients with recurrent cerebrovascular disease (10.4% of patients in the statin group had a recurrent stroke as compared with 10.5% of patients in the placebo group). This finding has been related to the late inclusion of patients at a mean of 4.3 years after their stroke or TIA, at a moment when patients were less likely to have a stroke event and more likely to have a coronary event. Therefore, in patients with a prior stroke, statins likely reduced the incidence of coronary events, but there was no proof that statins reduced the incidence of recurrent strokes. On the basis of these results, and despite the fact

that evidence of the benefits of statins in the secondary prevention of stroke was lacking, the Food and Drug Administration approved simvastatin for stroke patients, independently of any measurement of LDL-C.

To address whether statins are beneficial for secondary stroke prevention The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial [95] was designed. The SPARCL trial randomly assigned 80 mg/day of either placebo or atorvastatin to 4731 patients with a history of non-disabling stroke or TIA in the preceding 1–6 months and with no CHD. Patients were required to have a baseline LDL-C of 100 to 190 mg/dL (2.6 to 4.9 mmol/L). The mean baseline LDL-C and total cholesterol levels were about 133 and 212 mg/dL. Patients with hemorrhagic stroke were included if they were deemed to be at risk for ischemic stroke or CHD. Patients were excluded if they had atrial fibrillation, other cardiac sources of embolism, or subarachnoid hemorrhage. After 5 years of follow up, atorvastatin reduced fatal or nonfatal stroke (11.2 versus 13.1 percent, adjusted hazard ratio [HR] 0.84, 95% CI 0.71-0.99, absolute risk reduction at five years 2.2 percent, 95% CI 0.2-4.2 percent), despite a small increase in the incidence of hemorrhagic stroke.

Moreover, a meta-analysis reviewed the literature through January 2011 and found that statins significantly reduced the risk of major cerebrovascular events (i.e., fatal and nonfatal strokes and transient ischemic attacks) compared with controls, both in patients with established cerebrovascular disease (odds ratio [OR] 0.83, 95% CI 0.75-0.91) and in those without prior cerebrovascular disease (OR 0.80, 95% CI 0.71-0.91) [96].

In conclusion, statin therapy reduced the risk of secondary ischemic stroke regardless of pretreatment blood cholesterol levels and therefore the ACC/AHA guidelines recommend high-intensity statin for patients with TIA or ischemic stroke of atherosclerotic origin [97].

For patients unable to tolerate high intensity statins, moderate intensity statin therapy is given instead.

1.5.2.5 Antiplatelet Therapy

Antiplatelet agents are used both during the acute phase of ischemic stroke and for secondary prevention. Specifically, antiplatelet agents are recommended for most stroke subtypes except cardio-embolic stroke. However, several questions remain unanswered: should a single agent or a combination of two or more agents be used, how long should maintenance treatment be continued for and when is the exact time to initiate treatment after an ischemic stroke.

Aspirin

The most commonly used antiplatelet agent is aspirin. Aspirin irreversibly inhibits cyclooxygenase, thus preventing the conversion of arachidonic acid to thromboxane A₂ (TXA₂). Thromboxane A₂ is a vasoconstrictor and stimulator of platelet aggregation. Platelets are inhibited for their full life cycle (5–7 days) after exposure to aspirin. Aspirin also inhibits prostacyclin activity and this inhibits platelet aggregation. Aspirin reduces recurrent AIS rather than reducing neurologic symptoms after the index stroke. This is why aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy.

Both the CAST [60] and IST trials [61] provided data on the acute use of aspirin after AIS. The CAST trial showed that 160 mg/day of aspirin reduced the risk of stroke recurrence and death in the first 28 days. In IST, 300 mg/day of aspirin reduced stroke recurrence within 14 days; however, had no effect on early mortality. In both of these trials there was a small increase in the risk of hemorrhagic transformation. When aspirin is initiated within 48 hours of AIS, the data showed a small but statistically significant decline in risk of mortality and morbidity. The AHA/ASA guidelines recommend the administration of aspirin in patients with AIS within 24 to 48 hours after onset and for those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later.

Several meta-analyses have shown the benefits of aspirin for secondary prevention. A meta-analysis of 16 placebo-controlled trials (17,000 individuals at high average risk) aspirin showed a reduction of about a fifth in total stroke (2.08% vs 2.54% per year, $p=0.002$)[98].

In a pooled analysis of 12 trials ($n=15,778$ participants) aspirin reduced the 6 week risk of recurrent ischemic stroke by about 60% (84 of 8452 participants in the aspirin group had an ischemic stroke vs 175 of 7326; hazard ratio [HR] 0.42, 95% CI 0.32-0.55, $p<0.0001$) and disabling or fatal ischemic stroke by about 70% (36 of 8452 vs 110 of 7326; 0.29, 0.20-0.42, $p<0.0001$), with greatest benefit noted in patients presenting with TIA or minor stroke (at 0-2 weeks, two of 6691 participants in the aspirin group with TIA or minor stroke had a disabling or fatal ischemic stroke vs 23 of 5726 in the control group, HR 0.07, 95% CI 0.02-0.31, $p=0.0004$; at 0-6 weeks, 14 vs 60 participants, 0.19, 0.11-0.34, $p<0.0001$)[99].

In addition to aspirin, there are several antiplatelet agents proven to be efficacious in preventing recurrent ischemic stroke or TIA. These include: clopidogrel and aspirin in combination with dipyridamole.

Clopidogrel

Clopidogrel inhibits platelets by irreversibly binding to adenosine diphosphate (ADP) receptors (P2Y₁₂) and blocking ADP-mediated platelet aggregation after CYP2C19-mediated pharmacological activation[100].

The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Event (CAPRIE) trial observed 8.7% RRR with clopidogrel compared to aspirin ($p = 0.043$) in terms of composite outcome of stroke/myocardial infarction (MI)/vascular death. However, subgroup analysis revealed that clopidogrel was similar to aspirin in patients with prior strokes [101].

Clopidogrel is given orally at a dose of 75 mg per day. Loading patients with AIS with 375 mg followed by 75 mg was considered safe with no increase in the risk of hemorrhagic transformation [102].

ASA Plus Dipyridamole

Dipyridamole has platelet-inhibiting properties due to inhibition of adenosine re-uptake and platelet phosphodiesterase (PDE). For secondary stroke prevention, it has also been suggested that the beneficial effects of dipyridamole are due to a combination of both indirect anti-inflammatory effects from leukotriene inhibition and antithrombotic effect when used in combination with aspirin. The European Stroke Prevention Study-2 (ESPS-2) compared

aspirin monotherapy, dipyridamole monotherapy, aspirin-dipyridamole combination therapy, and placebo in 6602 patients with ischemic stroke/ TIA [103].

This study demonstrated that the combination of aspirin 25 mg and dipyridamole 200 mg provided a significant risk reduction of secondary strokes by 37% when compared to placebo and 18% when compared to aspirin monotherapy [103].

The open-label ESPRIT trial enrolled patients with TIA/stroke within 6 months and reported that there was an ARR of 1% for recurrent AIS in patients taking aspirin plus dipyridamole as compared to subjects on aspirin monotherapy[104].

The ESPRIT trial reported unexpected 42% reduction in major bleeding with the combination. In the non-inferiority PROFESS trial, where subjects were randomized to receive either aspirin plus dipyridamole or clopidogrel, no significant difference was found in the recurrent-stroke risks between the two treatments [85].

Finally, aspirin plus dipyridamole is less well tolerated than other antiplatelet therapy, primarily because of headaches, leading to declining popularity over the years. Moreover, dipyridamole is contraindicated in patients with coronary artery disease. New recommendation is promiosinhg for the use of Ticagrelor.

Ticagrelor

Ticagrelor has been recently used in combination with aspirin and shows a promising treatment option which is even a more effective DAPT combination, without non-responders and without a clinically unacceptable risk of severe bleeding events. Ticagrelor has unique pharmacological property since it is a reversible binding, direct-acting, oral P2Y₁₂ receptor

antagonist that prevents adenosine diphosphate-mediated P2Y₁₂ dependent platelet activation and aggregation [105]. Ticagrelor has a faster onset and achieves greater and more consistent platelet inhibition than clopidogrel, which requires metabolism to its active form [106, 107]. Although data are not yet sufficient to make routine therapeutic recommendations based on the pharmacogenomics of antiplatelet drug activity [108, 109], Ticagrelor could be used when clopidogrel is contraindicated or patients have resistance to clopidogrel.

2. OBJECTIVES

The first objective was to assess the adherence to international acute treatment guidelines of ischemic stroke in Lebanese hospitals and its impact on in-hospital mortality.

The second objective was to assess appropriateness of hypertension treatment in acute stroke and its adherence with the choice of medications tailored according to blood pressure readings.

The third objective was to investigate the degree of physician adherence with the international guidelines for post-stroke discharge medications among Lebanese hospitals.

3. Overview of The Manuscripts

3.1 First Manuscript

3.1.1 Introduction

Acute medical management is the one of the most influential factors on mortality rate and functional outcomes post-ischemic stroke. Implementing acute ischemic stroke management

protocols decrease the risk of stroke-related complications and improve outcomes. Acute supportive treatment should be instituted for all patients with stroke to ensure maximal perfusion and oxygenation of the brain. However, the in-hospital mortality is still high despite guidelines implementation. Moreover, studies that assess the adherence to treatment guidelines and its impact on the outcomes of ischemic stroke are limited.

Thus, this is the first study that was conducted in Lebanon to assess guidelines adherence in the acute management of ischemic stroke and evaluate its impact on in-hospital mortality.

3.1.2 Conclusion

The study findings highlighted that adherence to guidelines was suboptimal in the majority of the subjects that might explain the high death rates among stroke patients. The adherence to the various strategic treatment arms was not the same where it was high for the early performance of brain imaging and low for the emergency reperfusion. There are various reasons that explain the in-adherence to the guidelines in Lebanese hospitals due to the limited stroke units and even such units are mainly restricted in university hospitals. In addition, the financial issues play a major role in the choice of the treatment regimens due to the lack of reimbursement by social security or insurance.

3.1.3 Future research perspective

The findings of this study raised the need to assess the guidelines adherence to hypertension treatment in acute ischemic stroke matched according to blood pressure levels. Treatment of hypertension in acute ischemic stroke is still controversial since it has been documented that both high and low blood pressures are associated with detrimental consequences. Thus, we

conducted another study to assess appropriateness of hypertension treatment in acute stroke and evaluate the adherence with the choice of medications tailored according to blood pressure readings.

3.2 Second Manuscript

3.2.1 Introduction

Majority of ischemic stroke patients present with elevated blood pressure within 1 hour of symptom onset [110]. The elevation in blood pressure can affect the choice of subsequent treatment options where hypertension can affect thrombolytic eligibility and cause a delay in the administration of IV tissue plasminogen activator (IV tPA)[111]. Appropriate treatment of hypertension is extremely crucial in patients who have door-to-treatment times less than the recommended 60 minutes where timely and thus are eligible for IV tPA[112]. Due to the controversial areas surrounding hypertension management in acute ischemic stroke, thus this study aims to assess appropriateness of hypertension treatment in acute stroke and its adherence with the choice of medications tailored according to blood pressure readings.

3.2.2 Conclusion

This study demonstrates an evaluation of guidelines adherence to the treatment of hypertension in acute stroke. Our results showed that the majority of the patients received agents that were not recommended by the guidelines like labetalol or nicardipine. Labetalol was reserved for patients presenting with a high baseline blood pressure while other agents were given at much lower baseline blood pressure. Moreover, Labetalol, Amlodipine, and Nitroglycerine were the most effective medications on lowering systolic blood pressure and

Labetalol and Ramipril were effective on lowering the diastolic blood pressure. In addition, the subjects were overtreated for hypertension and a minority of the patients presented with blood pressure levels that required anti-hypertensive therapy. The study findings highlight the fact that the anti-hypertensive medications used in this study were not in accordance with the guidelines recommendations where Amlodipine and Trinitrine (nitroglycerine) are highly used. However, recommended agents by the guidelines as Labetalol and Nicardipine were underutilized. This can be explained by the lack of original diagnosis of stroke where in most cases it can be confused with other hypertensive or neurological conditions which explains the use of such agents especially nitrates. Arch *et al.* identified that around 20% of stroke cases are misdiagnosed which increases the administration of hypertensive agents and antiplatelet therapy [113]. Our results show that Labetalol was highly used at higher baseline blood pressures compared to Amlodipine and Trinitrine which support that the choice of antihypertensive medications is highly related with the baseline blood pressure.

Another major finding is the lack of adherence in terms of the initiation of antihypertensive medications tailored according to the blood pressure levels. However, the majority of the patients received antihypertensive medications even though they do not meet the criteria for treatment. Almost all patients who were eligible for blood pressure treatment received antihypertensive medication which sheds light that the guidelines were broadly followed for patients who required blood pressure treatment and that undertreatment rate was 10 %. A possible reason this patient did not receive treatment could be due to the isolated elevation of DBP of 120 mmHg, and SBP of 180 mmHg. Our results are consistent with a study done in Cameroon showing an undertreatment rate of 9.7% [114].

3.2.3 Future research perspective

The study findings reflected by the suboptimal adherence for hypertension management in acute stroke which raised the need to assess the guidelines adherence among stroke survivors. Effective secondary prevention is a cornerstone in stroke management since it minimizes complications and optimizes therapeutic outcomes. In addition, post stroke treatment adherence as it is associated with reduced disability and mortality. Furthermore, assessment of post-ischemic stroke management is vital since there are different medications prescribed for stroke survivor patients tailored to treat the underlying risk factors and concomitant disease states.

3.3 Third manuscript

3.3.1 Introduction

Guidelines adherence to stroke secondary preventive medications is subjected to challenges. Success of preventative measures and the reduction in stroke recurrence risk requires implementation of lifestyle factors, and initiation of medications immediately after the event and continuing the medications over the long-term period [115]. Early implementation of effective secondary prevention measures aimed at reducing blood pressure through anti-hypertensive medications, improving the lipid panel through statins, controlling glycemic level through antidiabetic drugs, and improving blood flow through anti-thrombotics is recommended to reduce the risk of further stroke events [95, 116-118].

Despite the growing evidence on the effectiveness of pharmacotherapies for the treatment and prevention of stroke, nonadherence to medications among stroke survivors remains a concern and is associated with adverse outcomes [119]. In order to better understand the

extent and nature of adherence, we conducted this study. Hence, the aim of this study is to investigate the physician adherence to post discharge stroke treatment guidelines including an assessment of prescribing the following medications as anti-thrombotic, anti-hypertensive, and lipid lowering agents upon hospital discharge. In addition, the study evaluates the change in blood pressure at different time intervals post anti-hypertensive administration among in-patients.

3.3.2 Conclusion

The results of this article highlight that non-adherence to post-discharge stroke medications is highly prevalent and that the international expert guidelines are also documented to be non-implemented in Lebanon probably because the recommended resources are not compatible with the resources available. The study concludes that the majority of the patients were not prescribed all the recommended medications upon discharge that emphasize a major gap in the adherence with the treatment guidelines. Furthermore, the study showed that systolic blood pressure is lowered from baseline, 2 hours, and 24 hours post treatment and diastolic blood pressure showed significant decrease only between baseline and 24 hours after treatment. In addition, further lowering in blood pressure was not associated with better therapeutic outcomes.

The findings of this study can be interpreted by the fact that physicians are unaware about the recommendations for secondary prevention after stroke [120] or the guidelines do not fit with patients' complex conditions and are poorly adapted to general practice[121, 122].

Barriers to the suboptimal guidelines adherence include, but are not limited to, lack of early symptoms recognition and delayed presentation after symptoms onset, financial constraints imposed on most of the Lebanese population, lack of drug and imaging modality availability (CTs), and provider related barriers (knowledge, experience, and fear of serious complications) [53]. In addition, there are other potential perceived barriers behind physician in-adherence can be lack of physician agreement with the recommendations due to lack of applicability or lack of evidence, environmental factors such as organizational constraints, and guideline factors such as unclear or ambiguous guideline recommendations.

4. Discussion

This study conducted over a two-year period highlighted that adherence to acute and post stroke treatment guidelines was suboptimal across different management strategies. In-adherence with the guidelines will be associated with a high degree of mortality since compliance with the treatment minimizes the development of complications. Our study was the first of its kind in Lebanon to date that assesses the adherence of Lebanese physicians to post discharge medications and acute stroke treatment guidelines. The insights described in this study allow the consideration of changes that could be manipulated in clinical practice to implement treatment guidelines.

Our findings highlight that guidelines were not applied that can be due to physician's unawareness to the treatment guidelines, unavailability of the medications at the Lebanese hospitals, and avoidance of drug prescription due to both fear from polypharmacy in stroke patients who are mainly elderly and the costs associated with some effective treatment

options. One of the striking findings in this study is the limited use of reperfusion therapy whether thrombectomy performance or administration of recombinant tissue plasminogen activator (rt-PA) although they are the main stay of acute treatment in acute stroke due to the limited availability of stroke units in Lebanon. Reperfusion therapy is the main stay of therapy, however, it is underutilized. The reason behind this limited use of reperfusion therapy is multi-factorial and can be due to either physician reluctant in the administration of this high-risk drug or patients are presenting beyond the time frame for eligibility criteria for drug administration. Furthermore, physicians concern about the risk of hemorrhage and the insecurity to use such a high-risk intravenous drug with poor physician compensation are associated also with restricted use of rt-PA. rt-PA should be utilized as a cornerstone in the treatment of all acute stroke patients as it allows for a fast recovery, shortens hospital stay, and decreases mortality rate. In addition, this study highlights that most of the patients were not treated according to the guidelines recommendations that can explain the reason for a high degree of complications post stroke. In this study, some areas in the acute treatment guidelines were applied to most of the patients as the performance of early diagnostic imaging, controlling diabetes, and lowering temperature in febrile conditions. However, other strategic treatment option was not performed according to the guideline's recommendations in most of the patients as treatment of hypertension. Hypertension, the most common symptom diagnosed in ischemic stroke, was not treated in accordance with guidelines recommendations. Our results showed that the majority of the patients received agents that were not recommended by the guidelines like vasodilator (Nitroglycerin). A major contributing factor to this result can be explained either by lack or delay in stroke diagnosis when patients are admitted to emergency department. In addition, in other cases there is

confusion between diagnosis of ischemic stroke patients presenting with hypertension and hypertensive emergencies or other neurological disorders. Furthermore, our results highlighted that acute ischemic stroke patients were prescribed anti-hypertensive medications that were not recommended by the guidelines and antihypertensive drugs were prescribed albeit that the blood pressure readings were not high enough to recommend hypertension management.

5. Research Programs

5.1 Strategies to Enhance Patient Adherence and Education

Future research programs should be based upon assessing knowledge and awareness about warning symptoms of stroke, risk factors, and disease etiology through a scale that should be validated and adapted to the Lebanese population. The scale should incorporate also awareness about the acute and rapid measures that should be performed directly in response to stroke symptoms. It is well known from previous literature that stroke can be prevented through appropriate awareness directed on identifying and modifying associated risk factors, initiating prophylactic measures, and increasing patient's education. Thus, prospective study can be done to assess and evaluate the knowledge about stroke and highlight the major gaps in stroke awareness. Thus, results from the future study can raise the need for implementing educational programs directed towards the community to improve patients' quality of life, prevent health-care professionals from being overwhelmed when stroke cases present to the emergency room at an early stage. As shown in the below figure, a future study can be conducted to focus on enhance patient education about awareness through simplifying

regimen characteristics through, imparting knowledge, modifying patient beliefs, enhancing patient and family communication, and evaluating medication adherence.

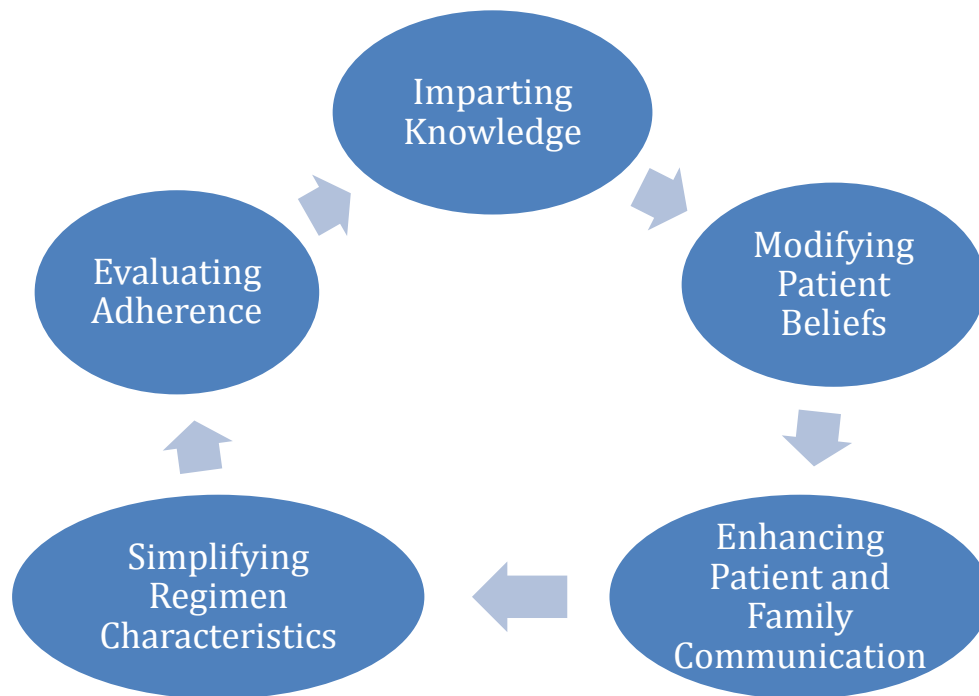


Figure 2. Framework representing the interventions to enhance patient education and ensure adherence to medications

One of the factors that can impact adherence to medications is the simplifying treatment characteristics. The prescribed treatment regimens should be simple and tailored according to patient’s daily life activities. Different adherence aids can be provided to help patient’s memory as medication boxes and alarms[123].

A cornerstone in minimizing and preventing disease progression in general and stroke specifically is through imparting appropriate knowledge. Ensuring adequate patient

understanding is associated with favorable outcome represented by enhanced medication adherence, improved satisfaction, and enriched recall [124].

Another important area that should be addressed is to enhance patient awareness through addressing patients' belief and intentions. Targeting patient knowledge alone is not adequate to enhance adherence but there is strong evidence which supports the fact that addressing patients' belief plays a synergistic effect in enhancing further treatment adherence[125].

In addition, encompassing and encouraging physician-patient communication plays a vital role in raising the level of awareness which increases the need to ask patients about their feelings and concerns. Thus, certain diseases can be missed by physicians due to the lack of proper communication and some patients rate that their relationship with physicians as poor because of their malpractice and miscommunication [126].

Thus, the findings of our study raise the need to conduct a future study in Lebanon to assess patient educational level about stroke and identify the factors associated with inadequate knowledge and in-adherence to medications.

5.2. Measuring and Improving Physician Adherence with International Guidelines

Clinical practice guidelines (CPGs) are systematically developed statements that assist clinicians in making decisions about appropriate patient care for specific clinical circumstances[127].

Guidelines development is a cornerstone in the management of critical illness as their implementation should improve quality of care by decreasing inappropriate variation, decrease mortality by expediting the application of effective advances to everyday practice, and should exert a positive impact on clinical workflow [128, 129]. Clinical practice guidelines are formulated based upon solid evidence that incorporates complicated clinical knowledge which is considered challenging to clearly comprehend and apply the guidelines in a proper manner into clinical tasks. The application of guidelines in the clinical setting is being hindered by many factors that impede the guidelines implementation. It is extremely important to identify and remove the road-blocks responsible for guidelines in-adherence. Accordingly, the key issues that are responsible for in-adherence with the guidelines should be addressed to ensure and optimize the application of the guidelines in every clinical situation. Thus, based upon a thorough revision of all the factors that may play a role with physicians in-adherence with the guidelines, a theoretical framework is being built as depicted below to clearly identify and manipulate the gaps.

One of the factors that may play a role in physician noncompliance could be related to physician attitudes toward the guideline leading to rejection. The attitudes can be explained by the lack of motivation, lack of self-efficacy, and lack of outcome expectancy. Behavior is

another factor that can impede guidelines in-adherence which can be related to the limitations of the guideline by itself or its implementation strategy, external barriers related to the inefficiencies in the hospital or health care delivery system, or to differences in the patient's clinical status.

Another important aspect that interferes with guidelines in-adherence is the physician knowledge represented by lack of awareness and lack of familiarity. The vast growth and expansion of research makes it difficult for physicians to be aware of guidelines implementation and critically apply to practice [130, 131]. It has been highlighted that awareness to the guidelines does not guarantee familiarity with the recommendation and its application correctly where lack of familiarity is more common than lack of awareness[132].

Physician attitude is another factor that can hinder adherence to the guidelines manifested by lack of self-efficacy and lack of outcome. Low self-efficacy manifested by lack of confidence in ability to follow guidelines recommendations is highly associated with in-adherence [133]. Outcome expectancy plays a major role in guidelines adherence since if the physician has a negative belief that the recommendation set by the guidelines won't lead to an improved outcome adherence to the guidelines will be low[134]. Thus, if physician's belief that the therapeutic intervention set by the guidelines won't play a role in the clinical setting, the adherence rate will be low.

Behavior factor also influences the degree of adherence since appropriate knowledge and positive attitude are not enough to ensure adherence to guidelines if there are external barriers[135]. The barriers that may be encountered and that limit the ability to adhere to the

guidelines pertain to patient, guideline, or environmental factors. Physicians usually document that the guidelines are not easy to follow or not convenient sometimes to apply on patients with multiple concomitant disease states and are polypharmacy.

In addition, lack of agreement with specific guidelines or the concept of guidelines in general can lead to in-adherence, although it is considered inferior factor compared to other factors[136].

Thus, the findings of our study raise the need to conduct a future study in Lebanon to assess and identify the barriers associated with guidelines in-adherence among physicians and then implementing measure to improve adherence based on the theoretical framework.

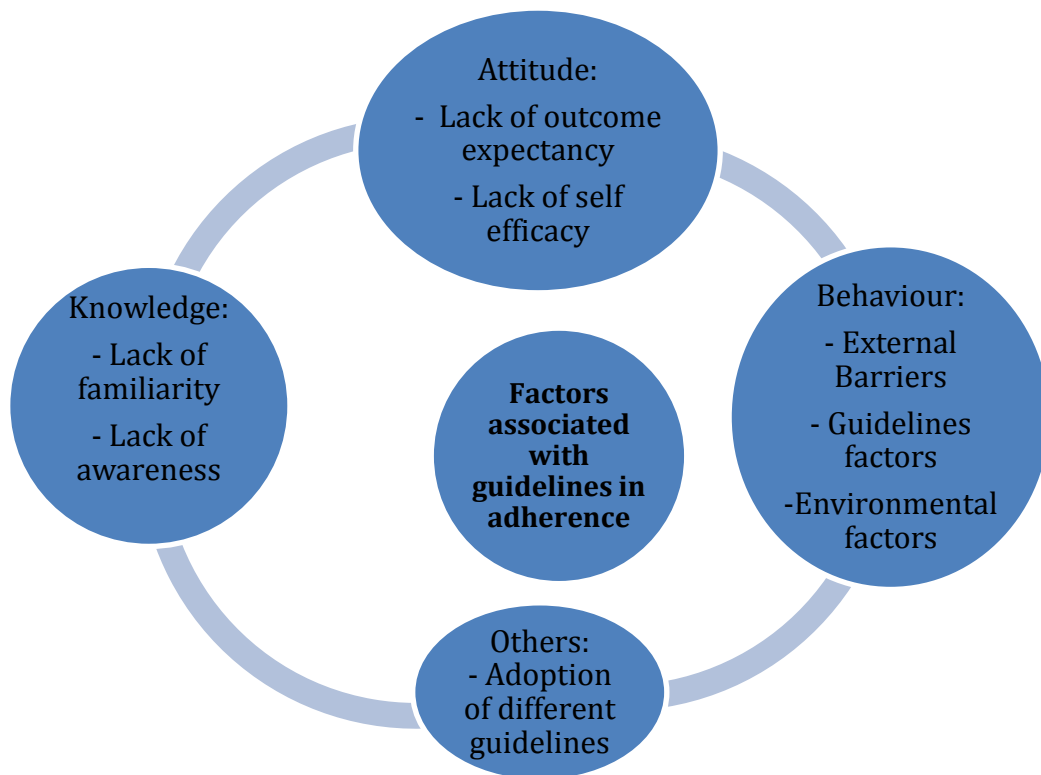


Figure 3. Theoretical framework responsible for guidelines in-adherence

6. LIMITATIONS AND STRENGTHS

6.1 Limitations

The major limitation of this study was its retrospective nature which can miss some data as the prescribed medications upon post discharge that could have been used in the study. Availability of incomplete data introduced information bias and affected the quality of the data obtained concerning acute and post discharge management as well as other factors that could affect the physician's approach to therapy like past medical history or past medication history or even the medications the patient may have taken at home just before admission. This also influenced our ability to include multivariable analysis as we were not able to account for confounding factors like age, gender, past medical history and the use of combination medications in the study. Another limitation was lack of hospital randomization since the researchers didn't have access to most hospitals due to the time needed to get an Institutional Review Boards approval; this may limit the sample and its external validity. In addition, the study enrolled a small sample size due to issues encountered with recruitment and finding stroke patients. The data collection phase also presented many biases, one of which was the selection bias as the patients were not randomly picked from the lists but in the order of their hospital identification numbers.

6.2 Strengths

This trial is the first of its kind in Lebanon that evaluates the adherence to both post discharge medications and acute stroke treatment guidelines among Lebanese physicians. The study is multi-center conducted in different hospitals (Makassed General Hospital, Rafic Hariri University Hospital, and Ain W Zein Medical Village) in Lebanon and from various regions of Lebanon. Moreover, the data collection sheet used is structured and facilitates the collection

of different kinds of information. Also, a statistician supervised all data entry and analysis. This study is vital as it assessed the guidelines adherence for acute hypertension management which is a controversial area closely linked with detrimental consequences associated with either extremely low or high blood pressure. The strengths of this study presents an introduction to the massive difference between clinical practice and guideline recommendations in acute settings where such issues can impose serious consequences. It also assessed rates of overtreatment and their effect on the stroke complications.

6.3 Clinical Implications

- * An evaluation of the guideline adherence and practice variations helps to fine tune the optimal care to ensure that the highest possible standard of practice is implemented.
- * Proper assessments of the relationship between the process of adherence to the guidelines and outcomes with a comprehensive set of process indicators will improve the quality of the care.
- * It is highly recommended to develop a specialty based clinical practice guidelines that can be applied on a national level considering the local needs to provide the best possible and evidence-based stroke care.

6.4 Lebanese Situation

Acute and post-stroke guidelines in-adherence is high among Lebanese physicians which is due to variety of factors. Most of the Lebanese hospitals lack the specialized Stroke Units which hinders the acute guidelines adherence and the utility of alteplase. In addition, financial

issues play a vital role in poor adherence with the guidelines since there is insufficient funds allocated for the management of critical conditions as stroke and physicians do not receive extra reimbursement when prescribing high-risk drugs as alteplase. There are other barriers that pertain to physicians including lack of physician awareness or lack of familiarity, lack of outcome expectancy, or the inertia of previous practice, or external barriers. Some of the Lebanese physicians do not receive grants or funds to attend international conferences to update and keep abreast of the new management options that limits the professional development and minimize the adherence with the guidelines. There is also striking occurrence of immigration of qualified physicians due to the financial crises and political scenarios Lebanon is witnessing that influenced the quality of medical case in Lebanese hospitals.

The limited prescription of alteplase among ischemic stroke Lebanese patients can be explained also by the fact that most of the patients either present beyond the time frame window for the use of alteplase or patients do not recall the time for symptom onset. Furthermore, Lebanon is a country where the medical insurance is expensive and restricted to patients of high-socioeconomic status. Also, the national social security fund is limited and doesn't grant approval for all therapeutic management strategies listed in the guidelines which further explains the low adherence with the guidelines. In Lebanon, there is mainly lack of public health policy due to certain factors as political that shows to interfere with the choice of the medications for the past years.

Another important aspect is that some hospitals restrict their formulary to some but not all pharmacological categories which pose an obligation on the physicians to treat patients with the available medications that depict the in-adherence with the guideline recommendations.

7. CONCLUSION

This study reveals the gap between AHA/ASA guideline recommendations and the clinical practice and the alarming rate of hypertension overtreatment. The key barrier for guidelines in-adherence in Lebanese stroke patients was the absence of social security insurance. In addition, increased concerns about medications costs and side effects in poly-pharmacy conditions also represented a major adherence barrier. It highlights the need for specified programs that monitor the conformity with guidelines and encourages hospitals and health care providers to implement the guidelines for providing optimal care. Adherence to the guidelines prevent the possible development of complications that could be life threatening like hemorrhage or neurological damage. It also highlights the fact the important role of a clinical pharmacist to promote and maintain adequate utilization of medications in both acute settings and upon discharge.

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Conflict of interest

The authors have no conflict of interest to disclose.

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Appendices

Appendix A: Article One

Adherence To International Guidelines

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Management of Acute Stroke Among Lebanese Patients: Assessing Adherence To International Guidelines

ABSTRACT

Objective: Ischemic stroke accounts for around 87% of all strokes worldwide and is the second leading cause of mortality and a significant factor of disability in adults. The objective of this study was to assess the adherence to international treatment guidelines of ischemic stroke in Lebanese hospitals and its impact on in-hospital mortality.

Material and Methods: This retrospective observational study was conducted in three Lebanese hospitals between January 2018 and December 2019.

Results: A total of 292 patients were included in this study with a mean age of 76.5 years and 56.8% were females and hypertension being the most prevalent comorbidity.

Brain imaging was performed upon admission in the majority of the patients and only 2.1% of the received intravenous fibrinolytic therapy. The adherence to guidelines recommendations for the correct dose, duration, and frequency for Labetalol was 50%. Hyperglycemia was reported among 26% of the study subjects and almost all 97.4% were treated to achieve a blood glucose level of 140 to 180 mg/dl. Total antiplatelet treatment adherence was documented in 6.2% of the enrolled subjects only where Aspirin was initiated within 24 to 48 hours after stroke in 87% and clopidogrel in 43.2%. The results highlighted that right sided hemiparesis, decreased level of consciousness, and hyperthermia were significantly associated with higher in hospital death. Guidelines in adherence for all the acute treatment measures and management strategies was 90.2%.

Conclusions: The findings of this research revealed inappropriate adherence to acute stroke treatment in the studied sample.

Introduction

Ischemic stroke is neurologic dysfunction caused by sudden embolic occlusions in the cerebral vessels^{1,2}. It accounts for around 87% of all strokes worldwide³ and is the second leading cause of mortality and a significant factor of disability in adults⁴. In Lebanon, the adjusted prevalence of stroke is 0.5%⁵, and the cumulative mortality rates are 14.1% at one month⁶.

Acute medical management and preexisting neurological complications are the most influential factors on mortality rate and functional outcomes post-ischemic stroke^{7,8}.

Complications occur within the first 4 days of acute ischemic stroke and include hyperthermia, myocardial infarction, deep venous thrombosis, extra-cranial bleeding, and pain⁹⁻¹¹. The most serious complications are pneumonia, and death^{8,10}. Studies suggest that implementing acute ischemic stroke management protocols decrease the risk of stroke-related complications and improve outcomes^{12,13}. However, the in-hospital mortality remains between 3 and 18% despite guidelines implementation¹⁴⁻¹⁹. Moreover, studies that assess the adherence to treatment guidelines and its impact on the outcomes of ischemic stroke are limited²⁰.

The acute management of ischemic stroke aims at minimizing brain injury, managing complications, and uncovering the pathophysiological basis of patients' symptoms²¹. Studies have revealed that adherence to acute stroke treatment guidelines is rarely applied by physicians and influenced by length of hospital stay, admission days whether on working days or during the weekend, age, gender, and patient prognosis upon presentation²²⁻²⁵. Indeed, older patients and women are less likely to receive thrombolytic therapy and be admitted to a specialized stroke treatment unit^{26,27}. Also, according to an international study conducted across different countries which showed that only 17% were adherent with the early use of

recombinant tissue-type plasminogen activator (rtPA), and 98% for antithrombotic prescription²⁸.

Acute treatment of stroke is vital as it decreases complications resulting from treatment in adherence. Although various studies assessed the prevalence of stroke survivors, predictors of death post-stroke, and adherence to post-discharge treatment guidelines^{5,6,29}, yet no data is available on the adherence to the acute management of ischemic stroke in Lebanon. Therefore, the objective of the study was to assess the adherence to international treatment guidelines of ischemic stroke in Lebanese hospitals and its impact on in-hospital mortality.

Patient and Methods

Study design and study population

A retrospective observational study was conducted in Lebanese hospitals. The information was retrieved from patient medical records at each site. The study design was approved by the Institutional Review Board of the hospitals and informed consent was not obtained as the study was retrospective and did not pose any risk to the patients. However, data were stripped of any personal identifying information.

Inclusion and exclusion criteria

Patients diagnosed with ischemic stroke from January 2016 till December 2017 and treated for acute stroke were included in the study. No attempt was made to verify the accuracy of the diagnosis because the aim was to assess the appropriateness of the physician's adherence to the acute treatment of stroke. Patients were excluded if they had diagnosis of hemorrhagic stroke.

Data collection

Medical records review was performed on-site by the principal investigator, without interference or bias, using a structured data collection sheet divided into two parts. The first part included demographic characteristics of the patients, co-morbidities, allergies, social habits, past medical history, and the previous intake of medications. Laboratory data for cholesterol, triglycerides, International Normalized Ratio (INR), and blood glucose (BG) were recorded. The second part included measures of acute stroke treatment, including the assessment of blood pressure (BP) levels during hospitalization, type of antihypertensive medications administered, diagnostic modalities, administration of fibrinolytic therapy in eligible patients, and the antiplatelet medications. The international guideline “Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals” was used as a standard reference in this study to evaluate the adherence to acute-stroke treatment in the absence of local or hospital guidelines²¹. These guidelines recommend a stepwise approach for the management, mandating baseline assessment of vital signs, stabilization of airways, and an accurate diagnostic through non-contrast brain Computed Tomography or Magnetic Resonance Imaging. Then, the patient must be assessed for eligibility for treatment by intravenous thrombolysis by measuring the time between the onset of symptoms, which should be within 4.5 hours, and treatment of hypertension if BP above 180/110 mmHg. If the patient is not eligible for thrombolytic therapy, the guidelines recommended treatment for hypertension when the systolic blood pressure is > 220 mmHg or diastolic blood pressure > 120 mmHg. In addition to reperfusion therapy, antithrombotic therapy with aspirin should be initiated within 48 hours of stroke onset and at discharge, along with deep venous thrombosis and pulmonary embolism prophylaxis and lipid-lowering medications²¹. The guidelines also recommended checking the temperature and using antipyretics if it exceeds 38°C. Adherence to guidelines had been defined as the use of all these measures except if any strategy was contraindicated.

Study outcomes

The primary outcome was to evaluate the extent of physicians' adherence to the international guidelines for acute stroke treatment. The secondary outcome was to assess the impact of treatment adherence on in-hospital mortality.

Statistical analysis

The statistical analysis was performed using IBM Statistical Package for the Social Science software. Descriptive statistics were used to describe patient characteristics, with frequencies and percentages for categorical variables and mean \pm standard deviation for continuous variables. Univariate associations were assessed for statistically significant differences using the Chi-square test or Fisher's exact test for categorical variables, as appropriate. No logistic regression was performed since the study had missing values that could not be controlled by the researchers, as it was a retrospective study. All reported p-values were two-sided, with alpha set at a significance level of 0.05.

Results

A total of 292 patients were included in this study with a mean age of 76.5 ± 11.9 years, 56.8% were females, and the majority (69%) lived in Mount Lebanon governorate. The most prevalent comorbidity was hypertension (38.4%), followed by arrhythmia (19.2%), and the least was diabetes (17.1%). Table 1 summarizes patients' socio-demographic characteristics.

The majority of participants (94.5%) had undergone brain imaging upon admission, and only 2.1% of the 14.4% eligible for emergency reperfusion received rtPA. From the enrolled subjects, only 5.5% had BP readings above 185/110 mmHg, and 75% were treated with Labetalol at the correct dose and duration. The total adherence to guidelines recommendations for Labetalol treatment in terms of the correct dose, duration, and frequency was 50%. Only 14 patients (21.2%) of the patients who were not eligible for reperfusion (with BP > 220/120 mmHg) received Labetalol.

Hyperglycemia (BG > 180mg/dl) was reported among 76 patients (26%) and almost all of the participants (97.4%) were treated to achieve a BG level of 140 to 180 mg/dl.

Only 28 patients (9.6%) had hyperthermia and were treated with antipyretic medications.

Total antiplatelet treatment adherence was documented in 6.2% of the enrolled subjects only where aspirin was initiated within 24 to 48 hours after stroke in 254 patients (87%) and Clopidogrel in 126 patients (43.2%). Table 2 shows procedures performed upon hospital admission, including brain imaging, reperfusion therapy for eligible patients, and BP management.

Both married and divorced patients were associated with a lower risk of in-hospital mortality, 88.9%, and 66.7%, respectively. Table 3 summarizes the bivariate association between the socio-demographic characteristics of the patients and in-hospital mortality.

Several factors, including socio-demographic characteristics, symptoms, brain imaging, reperfusion therapy, BP, BG, hyperthermia, and antiplatelet therapy, were assessed for in-hospital mortality (table 4); higher in-hospital mortality was significantly associated with a decreased level of consciousness, right-sided hemiplegia, and hyperthermia.

Discussion

Acute ischemic stroke is a leading cause of mortality and disability and remains a severe and significant global health problem. Adhering to international recommendations is essential when managing an ischemic stroke during the acute phase to prevent complications. This study is the first in Lebanon to assess adherence to guidelines in the acute management of ischemic stroke and evaluate its impact on in-hospital mortality, and highlighted that adherence to guidelines was suboptimal in most of the cases, which explains high death rates among stroke patients.

Brain imaging

According to acute stroke treatment guidelines, brain imaging evaluation should be performed upon arrival to the hospital as it assesses the degree of brain injury, and differentiates ischemic from hemorrhagic stroke^{21,30,31}.

In our study, there was a high adherence to brain imaging guidelines which are in contrary with the results of a study conducted in Ontario, showing that only 27.3% of the patients had timely brain imaging³². Also, a study in the United States found that 41.7% of patients with suspected stroke who arrived within 2 hours of symptoms onset underwent neuroimaging within 25 minutes after hospital arrival³³. These two studies revealed low adherence to brain imaging guidelines, although patients arrived at the hospital within the time limit (2-4 hours)^{32,33}.

Reperfusion therapy

In this study, only 42 patients (14.4%) were eligible for emergency reperfusion, and 6 (2.1%) received rtPA. Several studies had confirmed the efficacy of thrombolytic therapy through restoring blood flow to ischemic, improving the clinical outcome, and recovery of acute ischemic stroke patients^{34,35,36}. Reperfusion therapy, including intravenous fibrinolytics and endovascular interventions, such as mechanical thrombectomy, is the only approved treatment for acute stroke. However, it must be administered within a narrow window time²¹, which explains the fact that the majority of stroke patients are not eligible as they are either admitted beyond this time-window (around 85%) or during an unspecified time from symptom onset^{37,38}. The low numbers of reperfusion therapy in eligible patients, whether by IV fibrinolytic therapy or thrombectomy, might be explained by the bleeding risk, requiring a close monitoring post-fibrinolytic therapy, and the limited stroke unit centers across certain countries like Lebanon.

Blood pressure management

Both hypotension and hypertension have prognostic significance for death and disability, as several studies have identified that elevated BP is an etiologic factor for cerebral edema, hemorrhage, and generally worse clinical outcomes following acute ischemic stroke^{39,40,41}. In our study, 5.5% were eligible for reperfusion therapy, while 22.6% were not. Both groups were treated with antihypertensive medications, thus demonstrating adherence to guidelines, contrary to the results of research conducted in Greater Cincinnati, where only 30% of patients were treated according to recommendations⁴². Another study revealed that antihypertensive medications were prescribed to 28.1% of patients to target levels lower than 185/110 mm Hg before administering fibrinolytic therapy⁴³. In our study, a lower proportion of patients required treatment with antihypertensive medications as recommended, probably attributed to the different socio-demographic and baseline characteristics of the enrolled participants. Labetalol was administered at the correct dose, duration, and frequency in 50% of the participants who were eligible for reperfusion and in 21.2% who were not, in agreement with the findings of a previous study highlighting that only 52% of the patients eligible for fibrinolytic therapy received Labetalol to achieve the target BP before reperfusion therapy was implemented⁴³. Overall, the management of hypertension in patients with ischemic stroke was consistent with the choice of medication guidelines but suboptimal in terms of the required frequency.

Blood glucose management

In our sample, almost all patients were treated to achieve a BG of 140-180 mg/dl, consistent with the targets set by the guidelines. Hyperglycemia contributes to brain injury through acidosis and free radical production that can increase infarct volume and edema^{21,44,45}. In a recent observational pilot study, BG levels were controlled in 33% of ischemic stroke patients, and the most commonly depicted therapeutic intervention was regular insulin administered as a sliding scale⁴⁶.

Hyperthermia management

Fever in ischemic stroke patients significantly increases metabolic demand, favors free radical production, and enhances neurotransmitter release contributing to brain injury^{47,48}. The evidence supports the fact that controlling temperature readings decreases mortality⁴⁹. In our study, optimal management of hyperthermia was performed for almost all patients by antipyretic medications as recommended by the guidelines, contrary to findings of a study conducted in five United States comprehensive stroke centers showing a lack of temperature assessment in the emergency department among 39% of ischemic stroke patients⁴⁶.

Antiplatelet therapy

In our study, aspirin was initiated within 24 to 48 hours after stroke onset in 87% of the patients, while Clopidogrel was administered only in 43.2%, in line with the results of another study conducted in Ethiopia revealing that aspirin was prescribed in 96.8% of the patients⁵⁰ and the mean interval of antiplatelet initiation after hospital admission was 24 hours. Other studies also reported that aspirin was the most frequently utilized drug in the management of stroke, and the mean interval for aspirin initiation was 1.2 ± 1.4 days respectively^{51,52}.

Factors associated with in-hospital mortality

There is no consensus regarding the predictors of mortality in acute ischemic stroke; thus, a definite scoring system for predicting mortality is still not practiced. Our results showed that right-sided hemiparesis, decreased level of consciousness, and hyperthermia were significantly associated with higher in-hospital death. Similarly, a Chinese study highlighted that a decreased level of consciousness was significantly associated with both a higher frequency of stroke-related complications and in-hospital mortality⁵³. Our results are also consistent with those of a retrospective cohort study, where the mortality rate increased proportionally with increased temperature⁵⁴.

Study limitations and strengths

The principal limitation of this study was its retrospective nature, leading to missing data, such as the accurate time from symptom onset till hospital presentation, and other baselines characteristics, especially BP and BG levels. Another limitation was the lack of hospital randomization since the researchers did not have access to most hospitals, due to the time needed to get the Institutional Review Board approval, thus limiting the sample and its external validity. The sample size was small, which may obscure the effect of some potential predictors that would have been identified with a larger sample.

However, this study has some strengths. It is the first in Lebanon to evaluate the adherence of Lebanese physicians to guidelines of acute stroke treatment. It is multi-centered, conducted in different hospitals from various regions using a structured data collection sheet. Also, a statistician supervised data entry and analysis.

Conclusion

The findings of this research revealed inappropriate adherence to acute stroke treatment. This raises the need for further studies with longer duration, and larger sample. This study highlights the urgent need to other risk factors that may increase stroke mortality in Lebanon.

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Declaration of interest

None

Conflicts of interest

The authors declare no conflicts of interest.

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Table 1: Socio-demographic characteristics of the patients enrolled in the study	
Socio-demographic characteristics	N (%)
Mean age ± Standard deviation	76.5 ± 11.9
Gender	
Male	126 (43.2%)
Female	166 (56.8%)
Dwelling Region	
Beirut	76 (26%)
Mount Lebanon	204 (69%)
South Lebanon	2 (0.7%)
Missing values	10 (3.4%)
Marital status	
Married	110 (37.7%)
Single	6 (2.1%)
Divorced	12 (4.1%)
Missing values	164 (56.2%)
BMI categories	
Underweight	4 (1.4%)
Normal	26 (8.9%)
Overweight	20 (6.8%)
Obese	24 (8.2%)
Missing values	218 (74.7%)
Past medical history	
Hypertension	112 (38.4%)
Stroke	54 (18.5%)
Diabetes	50 (17.1%)
Dyslipidemia	55 (18.8%)
Arrhythmia	56 (19.2%)

Table 2: Brain imaging, reperfusion therapy, BP management, and antiplatelet administration among the patients	
	N (%)
Brain imaging performance	
No	2 (0.7%)
Yes	276 (94.5%)
Missing values	14 (4.8%)
Patient candidate for emergency reperfusion and prescribed fibrinolytic therapy	
No	286 (97.9%)
Yes	6 (2.1%)
BP >185/110 mmHg and eligible for emergency reperfusion	
No	66 (22.6%)
Yes	16 (5.5%)
Missing values	210 (71.9%)
Total adherence to Labetalol dose, duration, and frequency	
No	10 (50%)

Yes	6 (50%)
BP >220/120 not eligible for emergency reperfusion and received Labetalol	
No	
Yes	46 (69.7%)
Missing values	14 (21.2%) 6 (9.1%)
Hyperglycemia treated	
No	2 (2.6%)
Yes	74 (97.4%)
Antipyretic medications administered to lower body temperature	28 (100%)
Aspirin administered within 24-48 hours post stroke	
No	4 (1.4%)
Yes	254 (87%)
Missing values	34 (11.6%)
Clopidogrel administered within 24-48 hours after stroke	
No	166 (56.8%)
Yes	126 (43.2%)
Total antiplatelet treatment adherence	
No	274 (93.8%)
Yes	18 (6.2%)
Total adherence to treatment measures and management strategies	
No	263 (90.2%)
Yes	29 (9.9%)
BP: Blood pressure	

Table 3: Associations between socio-demographic characteristics of the patients and in-hospital death

Characteristics	In-hospital death		P value
	No	Yes	
Gender			
Male	114 (91.9%)	10 (8.1%)	0.314
Female	136 (100%)	16 (10.5%)	
Dwelling region			
Beirut	58 (87.9%)	8 (12.1%)	0.573
Mount Lebanon	182 (91%)	18 (9%)	
South Lebanon	2 (100%)	0 (0%)	
Marital Status			
Married	96 (88.9%)	12 (11.1%)	0.055
Divorced/ widowed	8 (66.7%)	4 (33.3%)	
BMI categories			
Underweight	2 (100%)	0 (0%)	0.073
Normal	22 (91.7%)	2 (8.3%)	
Overweight	12 (75%)	4 (25%)	
Obese	22 (100%)	0 (0%)	

Table 4: Associations between the patients' symptoms, and acute performance management strategies and in-hospital death			
Symptoms	In hospital death		P value
	No	Yes	
Dysarthria			
No	174 (87.9%)	24 (12.1%)	0.072
Yes	76 (97.4%)	2 (2.3%)	
Right sided hemiplegia			
No	182 (88.3%)	24 (11.7%)	0.019
Yes	68 (97.1%)	2 (2.9%)	
Decreased level of consciousness			
No	200 (96.2%)	8 (3.8%)	<0.001
Yes	50 (73.5%)	18 (26.5%)	
Body temperature >38 °C			
No	224 (92.6%)	18 (7.4%)	0.02
Yes	20 (71.4%)	8 (28.6%)	

Appendix B:

Article Two

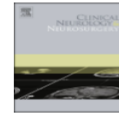
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Assessment of acute treatment of hypertension in ischemic stroke patients

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ABSTRACT

Objectives: Stroke, the most common neurologic disorder and the major cause of disability and death after heart disease causing 11.8% of the total deaths worldwide, is defined as a rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 h. This study aims to assess appropriateness of hypertension treatment in acute stroke and its adherence with the choice of medications tailored according to blood pressure readings.

Patients and methods: This was a pilot study performed in Lebanese hospitals where medical records of ischemic stroke patients were used to collect required data. The study enrolled ischemic stroke patients older than 18 years of age, admitted to intensive care unit or internal medicine department. Patients with hemorrhagic stroke were excluded. Statistical analysis was done using IBM Statistical Package for the Social Science software. The significance level is p -value ≤ 0.05 .

Results: A total of 146 patients (56.8% females; mean age 76.6 ± 11.9) were included in the analysis. At baseline, patients had a mean \pm standard deviation (SD) SBP of $160.6 (\pm 31.3)$ and a mean DBP of 85.5. Labetalol and amlodipine were administered to patients with significantly higher baseline blood pressure ($p < 0.001$). Change in SBP from baseline after 2 h of drug administration was significantly higher with labetalol ($p = 0.028$ for patients eligible for reperfusion), amlodipine ($p = 0.014$), and nitroglycerine ($p = 0.044$). As for the change in SBP after 24 h, it was significantly higher with labetalol just for patients not eligible for reperfusion ($p < 0.001$), and amlodipine ($p = 0.006$). As for the change in DBP, it was significantly lower after 24 h on labetalol administration for patients not eligible for reperfusion ($p < 0.001$) and it was also lower 2 h after administration of ramipril ($p = 0.001$) and 24 h ($p = 0.021$).

Conclusion: This study reveals the gap between American Stroke Association guideline recommendations and the clinical practice and states the impact of such a difference on patients' health.

1. Introduction

Stroke, the most common neurologic disorder and the major cause of disability and death after heart disease causing 11.8% of the total deaths worldwide, is defined as a rapidly developing [1] clinical signs of focal disturbance of cerebral function lasting more than 24 h. Stroke is classified as either ischemic or hemorrhagic in origin and around 87% of strokes are ischemic [2,3]. Ischemic stroke is caused by occlusion of a blood vessel in the brain, leading to diminished blood flow and subsequently ischemia. There are many etiologies that can lead to ischemic

stroke which are large-vessel atherosclerosis, cardioembolic source, small-vessel disease, other determined causes, and cryptogenic [4–6]. In addition, there are many risk factors associated with stroke which are categorized as either modifiable (smoking drug or alcohol use, obesity, and oral contraceptives use...) or non-modifiable (age, atrial fibrillation and gender...) [6–10]. The control of the reversible risk factors like diabetes, hyperlipidemia, atrial fibrillation, smoking, and hypertension reduce morbidity and mortality and improve quality of life. Effective tertiary prevention is based on the strict application of the guidelines given by the doctor to the patient which are mainly related

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to changes in lifestyle and specific medication [11].

According to the World Health organization, 84% and 16% of the patients die in low and high income countries respectively from ischemic stroke. The underlying reasons for the high prevalence of mortality from ischemic stroke are delayed brain neuroimaging performance upon hospital presentation, in-adherence to the prescription of anti-hypertensive medications, improper choice of anti-thrombotics, lack of rehabilitation, and preventative measures [2,10]. The current management guidelines focus mainly on reperfusion using intravenous thrombolytic medications, managing blood pressure (BP), and avoiding complications. Despite the controversy concerning BP management in patients with acute ischemic stroke (AIS) who are ineligible for thrombolysis, anti-hypertensives are recommended to lower systolic blood pressure (SBP) to readings below 185/110 mmHg prior to thrombolytic therapy and maintained below 180/105 for the next 24 h to reduce the risk of hemorrhagic transformation. The American Heart Association and American Stroke Association (AHA/ASA) guidelines suggest the use of intravenous nicardipine, labetalol, clevidipine or nitroprusside only if diastolic blood pressure (DBP) is above 140 mmHg. If patients are not eligible for reperfusion, anti-hypertensive therapy is administered if blood pressure is above 220/120 mmHg and a drop of 10–15% is expected in the next 24 h [12,13]. The choice of the antihypertensive therapy is controversial given that there are multiple non recommended medications such as nitroglycerine (NTG) that are highly utilized in cases of acute stroke [14,15]. Many studies have assessed overtreatment of hypertension in stroke patients in hospital settings and the risks associated with this treatment approach [15–17].

According to a study conducted by Baystate Medical Center which considered hypertension treatment appropriate in the setting of severe hypertension defined as systolic blood pressure (SBP) \geq 220 mmHg or mean arterial blood pressure MAP \geq 130 mmHg and potentially harmful in the setting of relative hypertension defined as SBP = 120 mmHg or MAP = 85 mmHg or absolute SBP = 90 mmHg or MAP = 60 mmHg. [18] Antihypertensive agents were given to 65% of patients at admission regardless of severity of hypertension and 42% of these had received therapy prior to admission. Severe hypertension was seen in 16% of the patients at baseline and 34% developed at least one episode of severe hypertension within 4 days of hospitalization [18]. In Lebanon there is lack of studies conducted to assess guidelines adherence for acute hypertension management in ischemic stroke so, this study aims to assess appropriateness of hypertension treatment in acute stroke and its adherence with the choice of medications tailored according to blood pressure readings.

2. Material and methods

2.1. Study design and population

This was a pilot study performed in Lebanese hospitals where medical records of ischemic stroke patients were used to collect required data. This study was approved by the Institutional Review Board of each site and by the ethics committee at The Lebanese International University. Three hospitals were enrolled to obtain the required cases where the number was divided almost equally between the hospitals to have a uniform patient distribution (50 patients from each hospital). Each involved study center generated a list of all ischemic stroke patients who were admitted and treated anti-hypertensive medications. Data was completely anonymous; names and other personal information were removed.

The study enrolled ischemic stroke patients older than 18 years of age, admitted to intensive care unit or internal medicine department. Patients with hemorrhagic stroke were excluded.

2.2. Data collection

Medical records review was performed on site by the principal investigator who had training about the data collection, without interference or bias, using a structured data collection sheet which was divided into two sections. The first included demographic characteristics of the patients, co-morbidities, allergies, and social habits. The second section included past medical history as well as the previous medications intake. Additional data was recorded about the baseline blood levels of cholesterol, triglycerides, and International Normalized Ratio (INR). Also, a detailed description of the blood pressure levels assessed through the systolic and diastolic reading done at baseline upon hospital admission, and then at 2 h and 24 h after hospitalization. The data collection sheet was inspired by a study done in Germany titled "Knowledge About Stroke Risk Factors: A Population Based Survey" [13].

According to ASA hypertension treatment guidelines, patients who are eligible for reperfusion should be treated if the blood pressure is above 185/110 and maintained below 180/105 for 24 h. However if thrombolysis is not an option, antihypertensive drugs should be administered if the BP reading is above 220/110 and the expected drop is 10–15% within the first 24 h after admission [12]. The antihypertensive dose and administration rate that were utilized in the study were the same as per the guidelines recommendations for the acute treatment of hypertension in acute ischemic stroke. Medications that were not consistent with the guidelines recommendations were dependent on the clinician opinion.

2.3. Outcomes

Primary outcome: Assessment of guidelines adherence for blood pressure management in acute stroke settings in terms of choice of antihypertensive agent, dose, and BP target levels.

Secondary outcomes: Blood pressure changes at 2 h and 24 h after administration of anti-hypertensive medications.

2.4. Statistical analysis

Statistical analysis was done using IBM Statistical Package for the Social Science software (SPSS version 21.0). Descriptive frequency tables were obtained to assess demographic data of the study population. Chi square and Fisher's exact testing was used to compare between the different antihypertensive medications used in the management of blood pressure in AIS and the change in blood pressure at 2 h and 24 h. Also *t*-test was used to compare mean blood pressures at baseline and at 2 h and 24 h after the administration of each antihypertensive medication. Missing data was not replaced since it formed less than 10% of the total data. The significance level is p -value \leq 0.05.

3. Results

3.1. Population characteristics

A total of 146 patients (56.8% females; mean age 76.6 ± 11.9) were included in the analysis. They were mainly residing in Mount Lebanon (72.3%) and Beirut (27%), and 24.7% were cigarette smokers versus 9.6% waterpipe smokers. Sociodemographic and lifestyle factors are represented in Table 1.

As seen in Table 2, a history of hypertension was most commonly reported in the sample (76.7%) followed by a history of atrial fibrillation (38.4%), hyperlipidemia (37.7%), stroke or TIA (37.5%), and diabetes mellitus (34.2%). As for the medication history, 41.1% of the patients were taking aspirin, 30.8% on lipid lowering agents, 65.5% on antihypertensive agents (mainly ACEI and CCBs), and 16.4% on vitamin K antagonists. More details are shown in Tables 2 and 3.

Table 1
Sociodemographic and lifestyle data.

Variable	Frequency (n)	Percentage (%)
Total number of subjects	146	100%
Gender		
Male	63	43.2%
Female	83	56.8%
BMI		
Underweight	2	5.4%
Normal	13	35.1%
Overweight	10	27.0%
Obese	12	32.4%
+ Residence area		
Beirut	38	27%
Mount Lebanon	102	72.3%
South Lebanon	1	0.7%
Cigarette smoker	36	24.7%
Waterpipe smoker	14	9.6%
Alcohol consumption	7	4.8%
	Mean	Standard Deviation
Weight in kg	71.2	± 18.3
Height in cm	160.3	± 8.6

Table 2
Past medical history of the study population.

Variable	Frequency (n)	Percentage (%)
HTN	112	76.7%
Stroke or TIA	54	37.5%
Atrial fibrillation	56	38.4%
Hyperlipidemia	55	37.7%
DM	50	34.2%
MI	21	14.4%
Dementia or cognitive impairment	7	4.8%
CHF	31	21.1%
Angina	42	28.8%
PCI without stent	5	3.4%
PCI with stent	12	8.2%
CABG	10	6.8%
Migraine	3	2.1%
Peripheral artery disease PAD	4	2.7%

Table 3
Medication history of the study population.

Variable	Frequency (n)	Percentage (%)
Anticoagulants		
LMWH	1	0.7%
Vitamin k antagonist	24	16.4%
Direct oral anticoagulants	10	6.8%
Antiplatelets		
Aspirin	60	41.1%
Clopidogrel	17	11.7%
Lipid Lowering agents	45	30.8%
Antihypertensive		
None	50	34.5%
1 drug	25	31.0%
2 drugs	8	17.2%
3 drugs		5.5%
Antihypertensive drugs		
Beta blocker	17	11.6%
Calcium channel blocker	37	25.3%
ACEI	39	26.7%
ARB	15	10.3%
Alpha blocker	0	0%
Thiazide diuretic	8	5.5%
Loop diuretic	3	2.1%
Nitroglycerine	0	0%

3.2. Antihypertensive agents choice and outcome

At baseline, patients had a mean \pm standard deviation (SD) SBP of 160.6 (\pm 31.3) and a mean DBP of 85.5 (\pm 14.9). After 2 h and 24 h, mean SBP decreased to 140.3 (\pm 23.4) and 138 (\pm 21.3) and DBP to 78.9 (\pm 14.5) and 74.1 (\pm 12.1), respectively. Concerning antihypertensive therapy in the acute phase, labetalol was administered to 13.9% of patients eligible for reperfusion and to 8% of those not eligible for reperfusion. The dose and rate of administration were coherent with the tables listed in the guideline in 46.2% and 50% of the cases respectively. Nicardipine was administered to 2 patients (1.4%) of the entire population whereas sodium nitroprusside was not administered to any patient in the sample. Most commonly used antihypertensive agents in the acute setting were amlodipine (31.9%), followed by nitroglycerin (trinitrine with nitroglycerin; 23.7%), and ramipril (11.1%). Finally, the least used antihypertensives were angiotensin receptor antagonists ARBs (candesartan and telmisartan; 0.7%).

3.3. Assessment relative to baseline blood pressure

As shown in Table 4, labetalol and amlodipine were administered to patients with significantly higher blood pressure at baseline ($p < 0.001$), irrespective of their eligibility for reperfusion.

Tables 5 and 6 represent the decrease in blood pressure after 2 and 24 h after the initiation of antihypertensive agents. As seen in Table 5, change in SBP from baseline after 2 h of drug administration was significant. Nicardipine was administered to 2 patients (1.4%) of the entire population whereas sodium nitroprusside was not administered to any patient in the sample. Most commonly used antihypertensive agents in the acute setting were amlodipine (31.9%), followed by nitroglycerin (trinitrine with nitroglycerin; 23.7%), and ramipril (11.1%). Finally, the least used antihypertensives were angiotensin receptor antagonists ARBs (candesartan and telmisartan; 0.7%).

4. Discussion

This study demonstrates an evaluation of adherence to the acute management of AIS according to the ASA guidelines. Data concerning aspects of hypertension management during the first 24 h post admission were collected using a collection sheet. Our results showed that the majority of the patients received agents that were not recommended by the guideline like labetalol or nicardipine. Labetalol was reserved for patients presenting with a mean baseline blood pressure of 205/104 mm Hg while other agents were given to lower baseline BP ranging between 175 and 140/93 and 85 mm Hg. Moreover when studying the effect of utilization of these agents on blood pressure the highest impact on SBP was induced by Labetalol, amlodipine and nitroglycerine while that on DBP was induced by Labetalol and Ramipril.

4.1. Management of blood pressure

4.1.1. Choice of antihypertensive agent and outcome

The most striking finding is related to the choice of the antihypertensive agent. Recommended agents according to the guidelines like labetalol and nicardipine were underutilized (21.9% and 2.1% respectively). On the other hand amlodipine and nitroglycerine are highly used even though they are not mentioned in the guidelines (31.9% and 18.1% respectively). A major contributing factor to this result is the lack of prompt diagnosis of AIS in clinical settings where in most cases it can be confused with other hypertensive or neurological conditions. Different studies have identified 20% of stroke cases that can be missed but this more often happen in posterior circulation stroke than anterior circulation stroke and this might not lead to using BP lowering inappropriately [20–22]. Furthermore, the choice of the antihypertensive therapy is also influenced by the mean blood pressure at baseline. Baseline BP in labetalol users was 205.8/104 mm Hg compared with

Table 4
Administration of antihypertensive agents and blood pressure at baseline.

Type of antihypertensive administered		Systolic blood pressure change at baseline		p-value	Diastolic blood pressure at baseline		p-value
		Mean	Standard deviation		Mean	Standard deviation	
Labetalol (eligible for reperfusion)	Yes	205.8	± 11.8	< 0.001	104	± 6.5	0.001
	No	161.0	± 23.9		86.5	± 14.8	
Labetalol (not eligible for reperfusion)	Yes	209.7	± 34.4	< 0.001	103.9	± 10.7	< 0.001
	No	153.0	± 26.4		82.3	± 14.2	
Nicardipine (not eligible for reperfusion)	Yes	165	± 63.6	0.894	90	± 14.1	0.653
	No	157.4	± 30.8		84.0	± 15.2	
Ramipril	Yes	164.1	± 22	0.530	93.3	± 12.4	0.016
	No	160.1	± 32.4		84.5	± 15.0	
Amlodipine	Yes	177.3	± 26.7	< 0.001	91.2	± 11.8	< 0.001
	No	152.6	± 30.4		82.8	± 15.5	
Trinitrine	Yes	175.0	± 25.6	0.004	89.5	± 12.0	0.085
	No	157.4	± 31.7		84.61	± 15.4	
Captopril	Yes	173.9	± 18.6	0.100	86.14	± 12.1	0.891
	No	159.9	± 31.8		85.46	± 15.1	
Furosemide	Yes	140	± 14.1	0.268	80	0	< 0.001
	No	160.8	± 31.5		85.57	± 15.0	
Nitroglycerine	Yes	163.4	± 41.3	0.846	86.87	± 19.8	0.843
	No	160.4	± 30.9		85.41	± 14.7	
Perindopril	Yes	158	± 33.3	0.917	80	± 20	0.676
	No	160	± 31.5		85.61	± 14.9	
Nebivolol	Yes	146.5	± 9.2	0.236	68.5	± 2.1	0.004
	No	160.8	± 31.5		85.74	± 14.9	
Bisoprolol	Yes	150	0	< 0.001	89.5	± 0.7	0.003
	No	160.1	± 31.9		85.11	± 15.3	

Table 5
Administration of antihypertensive agents and systolic blood pressure change after 2 h and 24 h.

Type of antihypertensive administered		Systolic blood pressure change at 2 h		p-value	Systolic blood pressure change at 24 h		p-value
		Mean	Standard deviation		Mean	Standard deviation	
Labetalol (eligible for reperfusion)	Yes	30.8	± 23.3	0.028	34.2	± 25.2	0.458
	No	11.6	± 14.5		24.7	± 19.1	
Labetalol (not eligible for reperfusion)	Yes	31.4	± 23.5	0.003	58.1	± 36.2	< 0.001
	No	9.5	± 21.8		19.4	± 25.3	
Nicardipine (not eligible for reperfusion)	Yes	10.0	± 28.3	0.926	10.0	± 28.3	0.632
	No	11.5	± 22.8		23.0	± 28.5	
Ramipril	Yes	10.1	± 16.3	0.653	21.7	± 21.3	0.671
	No	12.8	± 23.3		24.2	± 29.1	
Amlodipine	Yes	19.2	± 3.0	0.014	33.0	± 26.1	0.006
	No	9.0	± 2.5		19.2	± 28.3	
Trinitrine	Yes	20.5	± 18.6	0.044	32.84	± 24.9	0.062
	No	10.5	± 23.1		21.89	± 28.6	
Captopril	Yes	18.5	± 11.2	0.206	40.67	± 23.6	0.132
	No	12.2	± 22.9		23.15	± 28.2	
Furosemide	Yes	5.0	± 7.1	0.344	15	± 35.4	0.778
	No	12.6	± 22.1		24.07	± 28.2	
Nitroglycerine	Yes	0.3	± 29.5	0.141	8.14	± 50.3	0.002
	No	13.2	± 22.0		24.81	± 26.6	
Perindopril	Yes	6.0	± 19.7	0.615	35	± 18.0	0.391
	No	12.7	± 22.7		23.68	± 28.4	
Nebivolol	Yes	17.0	± 22.6	0.843	21	± 28.3	0.917
	No	12.5	± 22.6		23.96	± 28.3	
Bisoprolol	Yes	13.3	± 49.2	0.048	6.33	± 37.3	0.049

177.3/91.2 mm Hg for amlodipine and 175/89.5 mm Hg for nitroglycerine. A trial by Lakshminarayan et al. that showed increased level of guideline compliance in patients having higher blood pressure at baseline therefore a clearer diagnosis of hypertension associated with stroke [17]. Moreover, such results emphasize that guideline recommendations had little impact on real life practice because of the absence of clear targets or steps that guide therapy. Another article studied the effect of the adherence in acute ischemic stroke at hospital, found that patients hospitalized with acute ischemic stroke at get with the guidelines (GWTG)-Stroke hospitals had greater improvement of clinical outcomes over time, than at similar hospitals that did not participate in the GWTG-Stroke program [23].

Further analysis of the antihypertensive therapy regimen shows that in clinical practice there is a lack of compliance with the targets set by the American guidelines for the initiation of drug therapy upon admission. Given that the guidelines recommend treatment in patients with SBP of ≥ 220 (not receiving alteplase) or ≥ 185 (on alteplase), the majority of the patients received a form of therapy for hypertension. (1213) The mean baseline SBP for the population ranged between 150 and 160 mm Hg with only 8 patients had presented with BP above the levels requiring intervention. Many studies have shown an association between lower ranges of blood pressure and the risk of systemic hemorrhage and increased mortality. One Such study is Castillo et al. which discovered that for every 10 mmHg drop < 180 or

Table 6
Administration of antihypertensive agents and diastolic blood pressure change after 2 h and 24 h.

Type of antihypertensive administered	Diastolic blood pressure change at 2 h		p-value	Diastolic blood pressure change at 24 h			
	Mean	Standard deviation		Mean	Standard deviation	p-value	
Labetalol (eligible for reperfusion)	Yes	9.4	± 17.7	0.537	18.4		0.428
	No	5.9	± 9.0		13.6	± 12.6	
Labetalol (not eligible for reperfusion)	Yes	4.0	± 22.4	0.697	28.6	± 8.2	< 0.001
	No	6.9	± 14.8		10.3	± 16.3	
Nicardipine (not eligible for reperfusion)	Yes	5.0	± 7.1	0.796	30.0	± 14.1	0.311
	No	6.7	± 15.7		11.6	± 16.5	
Ramipril	Yes	19.6	± 13.2	0.001	21.4	± 15.5	0.021
	No	5.5	± 14.4		10.9	± 16.0	
Amlodipine	Yes	7.5	± 11.6	0.916	15.7	± 13.3	0.050
	No	7.2	± 16.5		10.4	± 17.4	
Trinitrine	Yes	9.0	± 12.8	0.468	14.7	± 12.6	0.300
	No	6.8	± 15.4		11.6	± 17.0	
Captopril	Yes	2.5	± 11.1	0.329	11.7	± 15.5	0.934
	No	7.5	± 15.1		12.2	± 16.4	
Furosemide	Yes	20.0	–	< 0.001	0.5	± 13.4	0.426
	No	7.1	± 15.0		12.4	± 16.3	
Nitroglycerine	Yes	0.6	± 17.5	0.261	8.1	± 30.1	0.499
	No	7.7	± 14.7		12.4	± 15.3	
Perindopril	Yes	9.0	± 15.7	0.865	10.3	± 19.5	0.881
	No	7.2	± 15.0		12.2	± 16.3	
Nebivolol	Yes	10.0	± 15.0	0.856	2.0	± 16.3	0.531
	No	7.3	± 15.0		12.3	± 16.3	
Bisoprolol	Yes	6.7	± 37.3	0.101	10.3	± 34.4	0.011
	No	7.9	± 14.4		12.9	± 14.9	

10 mm Hg \geq 180 the risk of early neurological deterioration increased 25% and 40% respectively so managing blood pressures lower than these values can increase the risk of complications [24]. On the other hand a study in 2015 addressing the use of nitrates patches in acute stroke management found adequate control of blood pressure using the patch but no effect on 90 day-prognosis [25]. According to a study conducted by Bavry et al., Candesartan was not associated with a reduction in vascular death, myocardial infarction, and stroke after 6 months of therapy compared to placebo but was significantly linked with lowering BP. In addition, Candesartan administration was associated with stroke progression and poor functional outcome compared to placebo [26].

Furthermore, according to the most recent study “ENCHANTED” which highlighted the findings that intensive blood pressure lowering is safe and associated with a reduction in intracranial hemorrhage but the reduction in bleeding did not lead to an improvement in clinical outcomes compared with guideline-recommended blood pressure treatment. In addition, intensive blood pressure lowering compared with current guideline-recommended blood pressure management was not associated with a significant difference in functional recovery, as assessed by a shift in the distribution of mRS scores at 90 days [27]. Hence, the results from the studies don't support a major shift towards the application of intensive blood pressure treatment in patients receiving alteplase for mild-to-moderate ischemic stroke as the extra-reduction in BP was not associated with a significant improvement in functional outcomes.

4.1.2. Blood pressure change at 2 h and 24 h from admission

The analysis performed on change in blood pressure at 2 h and 24 h showed that labetalol was able to induce a significant change in blood pressure at the 2 h interval and a milder drop at 24 h (30.8 mm Hg over 2 h to 34.2 mm Hg at 24 h) with p-values < 0.001. Also amlodipine and nitroglycerine provided a slower more sustained control over 2 h (19.2 mm Hg and 20.5 mm Hg) and 24 h (33 mm Hg and 32.8 mm Hg respectively) with p-values of < 0.001 for amlodipine and 0.002 for NTG. A study done by Kenji et al. showed that nitroglycerine when used in acute stroke to control BP induced a change within 10–15% as required by American guidelines. [28] The ASA guideline does not specify

a clear target for SBP and DBP drop which affects patient prognosis. However many studies have demonstrated the relationship between blood pressure change and poor outcomes [29–31]. Castillo et al. assessed this relation and found that a drop \geq 20 mm Hg in SBP within the first 24 h is associated with an early neurological deterioration [24]. Other studies have shown that a mild change in blood pressure within the first 24 h presented with favorable outcomes on mortality and prevention of long term neurological complications as identified by the guidelines [31–34].

Keizer et al. compared the effect of drop in Mean arterial pressure MAP on long term outcomes showed an increased risk of neurological deterioration in patients with a MAP < 90 mm Hg or > 130 mm Hg and favorable outcomes if MAP is between 90 and 109 mm Hg. [35] For the diastolic blood pressure ramipril and labetalol caused a significant change at 24 h (21.4 and 28.6 mm Hg respectively) from baseline but ramipril induced a sudden drop of 19.2 mm Hg at 2 h in comparison to labetalol that caused a mean of 9.4 mm Hg. The Intravenous Nimodipine West European Stroke Trial (INWEST) concluded that a decrease of \geq 10 mm Hg in diastolic blood pressure resulted in a worse prognosis [36].

4.1.3. Strengths and limitations of this study

To our knowledge this is the first study to assess guideline adherence in the management of hypertension in acute ischemic stroke settings in Lebanon. It sheds the light on the massive difference between clinical practice and guideline recommendations in acute settings were such issues can impose serious consequences, however further studies with bigger sample size and prospective design are needed to overcome the weaknesses of the current study.

However it had multiple limitations including it was a pilot study that included a small sample size due to issues with recruitment and finding stroke patients that affected the power of the study. The data collection phase also presented many biases, one of which was selection bias as the patients were not randomly picked from the lists but in the order of their hospital identification numbers. Moreover, the files used contained many missing values which introduced information bias and affected the quality of the data obtained concerning acute management as well as other factors that could affect the physician's approach to

therapy like past medical history or past medication history or even the medications the patient may have taken at home just before admission. This also influenced our ability to include multivariable analysis which meant that we did not account for confounding factors like age, gender, past medical history and the use of combination medications in the study.

5. Conclusion

This study reveals the gap between ASA guideline recommendations and the clinical practice and states the impact of such a difference on patients' health. It highlights the need for specified programs that monitor the conformity with guidelines and encourages hospitals and health care providers to follow them for providing the optimal care a patient's needs.

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Authors' contribution

Hiba AlHarfany and Lara Haidar contributed in data collection, Sarah Cherri and Diana Malaeb contributed in data analysis and in drafting the manuscript, Pascale Saleme and Hassan Hosseini contributed in supervising the article and in reviewing the final form of the manuscript.

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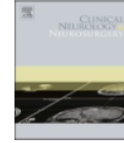
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Assessment of post discharge medication prescription among Lebanese patients with cerebral infarction: Results of a cross-sectional study



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ABSTRACT

Objectives: The study objective was to investigate the degree of physician adherence with the international guidelines for post-stroke discharge medications among Lebanese hospitals.

Patient and methods: This retrospective observational study was conducted in three Lebanese hospitals between January 2016 and December 2017.

Results: Out of 200 patients with stroke, 64.7 % were males. The difference of systolic blood pressure from baseline, 2 h, and after 24 h showed significant decrease by mean value 25.18 ± 33.45 ($P < 0.001$), and 6.44 ± 22.11 ($P = 0.019$) respectively. Also diastolic blood pressure showed significant decrease between baseline and after 24 h by a mean value 12.17 ± 13.63 ($P \text{ value} < 0.001$). Concerning post discharge medications adherence, antithrombotic drugs showed the highest percentage (73 %) followed by antihypertensive and lipid lowering agents by comparable results (47.5 % and 40.7 % respectively). The physician adherence for the three medications together showed (30.4 %).

Conclusion: Secondary prevention for critical diseases such as stroke appears to be inadequate in the study area.

1. Introduction

An ischemic stroke is a cerebrovascular incident, often a consequence of complete or partial obstruction of cerebral blood vessels [1]. More than 80 % of strokes are of an ischemic origin, and it has been estimated that around 80 % of stroke survivors continue to suffer from having to live with the sequelae of stroke (e.g., functional deficit) [2].

A study conducted in Lebanon shows that 25 % of patients that had been admitted into the hospital for stroke treatment had previously suffered from a stroke [3]. Therapy must be individualised to the patient, taking into account the presence of co-morbidities, modifiable and non-modifiable risk factors, as well as any external factors that might influence treatment approaches and decisions.

There is a multitude of causes that can lead to an ischemic stroke including small artery occlusive disease, cardioembolism,

microatheroma [4], and overall inadequate management of risk factors such as transient ischemic attacks ("mini stroke"), hypertension, diabetes, dyslipidemia, and smoking [5]. Generally, the risk of reoccurrence of a second cerebrovascular incident is highest during the first year following the stroke (12 %) [6]. Therefore, appropriate patient triage, risk-assessment, and commencement of secondary prevention approaches during the initial hospitalization for ischemic stroke are critical for decreasing the chances of stroke reoccurrence and improving overall patient clinical outcomes [7].

Despite the many benefits of implementing non-pharmacological interventions and life-style changes (e.g. smoking cessation since cigarette smoking is a major risk factor for the development of strokes, or incorporation of physical activity in overweight and obese patients), pharmacotherapy is often necessary and has demonstrated to improve survival rates, clinical outcomes, and reduce the risk of stroke

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reoccurrence in patients. This includes the use of blood pressure lowering agents, anti-platelet therapy, anti-coagulation therapy, and lipid-lowering agents [8]. Many of the pharmacological therapies recommended for primary prevention of ischemic strokes are also clinically suitable for secondary stroke prevention. Thus, to ensure suitable continuum of patient care post-discharge, interventions for the prevention of reoccurrence of cerebrovascular events should be initiated promptly in the acute setting and adequately maintained in the out-patient setting [3].

Successful continuum of secondary prevention depends on several factors including patient factors (e.g. perception towards the use of medicines, fear of side effects, ability to afford medicines, ineffectiveness, caregiver support, and cognitive well-being). Other factors include provider related aspects (e.g. proper patient counselling and communication, prescribing patterns), and system-level factors (e.g. hospital prescribing guidelines, insurance) [8]. It has been estimated that around 70 % of medication non-compliance is actually an intentional patient response to perceived unpleasant side effects, and high cost associated with long-term treatment.

The cross-risk after ischemic strokes for further complications highlights the importance of compliance to recommended treatment regimens. Multiple studies were conducted in order to gain a better understanding of how treatment is initiated, taking into account the factors influencing patient adherence and subsequently clinical outcomes. The Adherence eValuation After Ischemic Stroke Longitudinal (AVAIL) registry is a U.S. based study of stroke patient adherence to medications after hospital discharge. Patients are interviewed 3 months and 12 months after hospitalization, and the primary outcome of the study is to evaluate and document the current state of compliance and persistence to stroke prevention medications [8]. China National Stroke Registry (CNSR) Phase study is another hospital-based prospective study that was conducted in China with the same aim as the AVAIL study. Both AVAIL and CNSR reported that adherence was better in younger patients as compared to the elderly who suffer from multiple chronic co-morbidities and polypharmacy [9,10]. Data collected in both studies also suggested that patients who suffered from less severe stroke disability, and patients with overall higher family income, were more likely to have better long-term adherence and perseverance [11].

The results of the studies conducted stress the urgency and importance of adopting improved approaches for better management of stroke patients (risk factors, in-patient pharmacotherapy, out-patient maintenance preventive therapy). Therefore, further studies are required in order to identify barriers for physician medication adherence, and develop suitable interventions to encourage and improve the suitable use of evidence-based pharmacotherapies and minimize the risk of future stroke reoccurrence [12].

The purpose of this study was to investigate the degree of physician adherence with the international guidelines for post-stroke discharge medications among Lebanese hospitals and assess the impact of anti-hypertensive prescription on lowering blood pressure.

2. Patient and methods

2.1. Study design and study population

This was a retrospective observational study conducted in three Lebanese hospitals. Patient's information was obtained from the medical records of each site. The study design was approved by the Institutional Review Board of the three hospitals and by the ethics committee at the Lebanese International University. Informed consent was not obtained, as this was a retrospective study and did not pose any risk to the patients. However, data were stripped of any personal identifying information.

2.2. Inclusion and exclusion criteria

All adult patients diagnosed with ischemic stroke during the period from January 2016 till December 2017 and who were subsequently admitted to the internal medicine department or intensive care unit (ICU), or coronary care unit were included in the study. No attempt was made to verify the accuracy of the physician's diagnosis, because the aim was to assess the appropriateness of the physicians in the prescribing post-discharge stroke medications. Patients were excluded if they had haemorrhagic stroke diagnosis.

2.3. Data collection

Medical records review was performed on site by the principal investigator, without interference or bias, using a structured data collection sheet which was divided into three parts [Annex 1]. The first part included demographic characteristics of the patients, co-morbidities, allergies, and social habits. The second part included the past medical history including the previous medications intake. Additional data was recorded about the baseline blood levels of cholesterol, triglycerides, International Normalized Ratio (INR), and blood glucose. Also, a detailed description of the blood pressure levels assessed which were done at baseline upon hospital admission, and then 2 and 24 h post antihypertensive treatment.

In the absence of local or hospital guidelines, the international guideline "Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association" was used as a standard reference in this study to evaluate post-stroke discharge medications [12].

The guidelines recommendations for hypertension management mandates that the therapy is indicated for previously untreated patients with ischemic stroke who have an established blood pressure (BP) ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic several days post stroke. Initiation of therapy in lower BP targets is of uncertain benefits.

As for dyslipidemia management, statin therapy with intensive lipid-lowering effects is recommended in patients with ischemic stroke of atherosclerotic origin and an low density lipoprotein-cholesterol (LDL-C) level ≥ 100 mg/dl with or without evidence for other atherosclerotic cardiovascular disease and in case of LDL levels < 100 mg/dl without any evidence for atherosclerotic disease.

As for antiplatelet therapy, it is recommended to initiate a combination of Aspirin and Clopidogrel within 24 h of ischemic stroke and be continued for 21 days. However, for patients with a history of ischemic stroke or cardiovascular diseases, the usefulness of adding antiplatelet therapy to oral anticoagulant is of uncertain benefit.

Adherence to the guidelines was defined as the use of the following medications antihypertensive, lipid lowering, and antiplatelet drugs to all patients who survived the primary stroke with the absence of any contraindication to its prescription.

Systolic and diastolic blood pressure was assessed two and twenty four hours post antihypertensive medications [13].

2.4. Study outcomes

The primary outcome was the extent of adherence of the physicians to the international guidelines for post-stroke discharge medications.

Secondary outcome was to evaluate the impact of antihypertensive medications during hospitalization on lowering both the systolic and diastolic blood pressure which was assessed 2 and 24 h post treatment.

2.5. Statistical analysis

The statistical analysis was performed using IBM Statistical Package for the Social Science software (SPSS version 23.0). Descriptive statistics were used to describe patient characteristics, with frequencies and

Table 1
Socio-demographic characteristics of the study population.

Variable	Frequency (n)	Percentage (%)
Gender		
• Male	132	66
• Female	68	34
BMI^a		
• Normal	12	29.3
• Overweight	17	41.5
• Obese	12	29.3
Marital status		
• Single	39	21.1
• Married	139	75.1
• Divorced	7	3.8
Residence area		
• Beirut	108	60.3
• Mount Lebanon	33	18.4
• Bekaa	5	2.8
• North Lebanon	2	1.1
• South Lebanon	31	17.3
Cigarette smoker		
• Yes	99	48.5
Alcohol consumption		
• Yes	21	11.4
Physical activity	1	1

^a BMI: Body Mass Index.

percentages for categorical variables and mean \pm standard deviation for continuous variables. The two groups of patients were compared for statistically significant differences using chi-square or Fisher's exact tests for categorical variables, and Paired Sample T-test for continuous variables (blood pressure reading from the baseline, 2 and 24 h post treatment), as appropriate. Univariate associations were assessed for statistically significant differences using the Chi-square test or Fisher's exact test for categorical variables, as appropriate. All reported p-values are two-sided, with alpha set at a significance level of 0.05.

3. Results

3.1. Socio-demographic characteristics of participants

Among 204 participants 132 (64.7 %) were males and 68 (33.3 %) females. The mean age of the studied population was 65.4 ± 11.93 years. Concerning body mass index (BMI) categories, 12 (12.4 %) patients were normal, 17 (17.5 %) overweight and 12 (12.4 %) obese. The majority were smokers 99 (48.5 %), non-alcoholic 132 (64.7 %), married 139 (68.1 %), and living in Beirut district 108 (52.9 %). Only 1 (1 %) of the participants were physically active (Table 1).

3.2. Hospital characteristics

Regarding the hospital characteristics, 109 (53.4 %) of the participants were in private hospitals and 99 (48.5 %) were in hospital university settings (Table 2).

Table 2
Hospital Characteristics.

Variable	Frequency (n)	Percentage (%)
Hospital Setting		
• Private	109	53.4
• Public	95	46.6
Hospital University		
• Yes	99	48.5
• No	105	51.5

Table 3
Past medical history of the study population.

Variable	Frequency (n)	Percentage (%)
HTN ^a	74	77.1
Stroke or TIA ^b	26	27.1
Atrial fibrillation	12	12.5
Hyperlipidemia	19	19.8
DM ^c	44	45.8
MI ^d or CAD ^e	27	28.1
Dementia or Cognitive Impairment	11	11.5
CHF ^f	9	9.4
PCI ^g without stent	5	5.2
PCI ^g with stent	11	11.5
CABG ^h	4	4.2

^a HTN: Hypertension.

^b TIA: Transient Ischemic Attack.

^c DM: Diabetes Mellitus.

^d MI: Myocardial Infarction.

^e CAD: Coronary Artery Disease.

^f CHF: Congestive Heart Failure.

^g PCI: Percutaneous Coronary Intervention.

^h CABG: Coronary Artery Bypass Graft.

3.3. Past medical history

According to the past medical history, hypertension (HTN) showed the highest concomitant past medical history 74 (77 %), followed by stroke or transient ischemic attack (TIA) 26 (27.1 %), 12 (12.5 %) atrial fibrillation 19 (19.8 %) hyperlipidemia, and coronary artery bypass graft (CABG) 4 (4.2 %). On the other hand, none of the patients had previous angina pectoris, peripheral artery disease (PAD), migraine and family history of stroke or heart diseases (Table 3).

3.4. Past medication history

Regarding past medication history, 5 (5.7 %) of the patients were on oral vitamin K antagonist and one (1.1 %) was on low molecular weight heparin (LMWH). For anti-platelet drugs, 33 (38.8 %) were on Aspirin, and 15 (19.2 %) on Clopidogrel and 30 (36.1 %) of the patients on lipid lowering therapy. For anti-hypertensive drugs, 41 (55.4 %) of the participants were mainly on beta blockers and the least commonly prescribed was alpha blocker and 22 (25.3 %) of the patients were on dual antihypertensive drugs (Table 4).

3.5. Laboratory test

Regarding laboratory testing and vital signs, systolic and diastolic blood pressure, total cholesterol and LDL had almost normal mean values of 142.3 ± 27.45 , 76.31 ± 20.17 , 151.61 ± 44.44 , 107.61 ± 42.57 respectively. On the other hand, high density lipoprotein (HDL) was low with a mean value of 35.94 ± 7.92 and blood glucose, LDL and triglyceride were higher than the normal range values with mean values of 165.5 ± 104.9 , 107.61 ± 42.57 , 164.74 ± 80.94 respectively (Table 5).

3.6. Blood pressure descriptive analysis

The mean systolic blood pressure decreased significantly from baseline the time patient arrived to the hospital, 2 h and 24 h after antihypertensive treatment with a mean difference of 6.44 ± 22.11 (p-value of 0.019) and 25.18 ± 33.45 (p-value < 0.001) respectively. While on the other hand the mean diastolic blood pressure almost remained the same after 2 h and decreased significantly 24 h post treatment with a mean difference of zero (p-value of 0.159) and 12.71 ± 13.63 (p-value < 0.001) (Table 6).

Table 4
Medication history.

Variable	Frequency (n)	Percentage (%)
Anticoagulants		
Unfractionated heparin	0	0
LMWH ^a	1	1.1
Vitamin k antagonist	5	5.7
Antiplatelets		
Aspirin	33	38.8
Clopidogrel	15	19.2
Lipid Lowering Agents	30	36.1
Antihypertensive		
None	20	23
1 drug	22	40.2
2 drugs	19	65.5
3 drugs		87.4
Antihypertensive drugs:		
Beta blocker	41	55.4
Calcium Channel Blocker	25	33.8
ACEI ^b	19	25.7
ARB ^c	16	21.6
Alpha blocker	1	1.4
Thiazide diuretic	12	16.2
Loop diuretic	6	8.1
Nitroglycerine	1	1.4
Molsidomine	1	1.4

^a LMWH: Low Molecular Weight Heparin.^b ACEI: Angiotensin Converting Enzyme Inhibitors.^c ARB: Angiotensin Receptor Blocker.**Table 5**
Laboratory tests.

Variable	Mean ± standard deviation	Normal values
Blood Glucose	165.55 ± 104.9	70-127 mg
Systolic Blood Pressure	142.3 ± 27.45	< 140 mmHg
Diastolic Blood Pressure	76.31 ± 20.17	< 90 mmHg
Total cholesterol	151.61 ± 44.44	< 200 mg/dl
HDL ^a	35.94 ± 7.92	> 40 mg/dl
LDL ^b	107.61 ± 42.57	< 100 mg/dl
Triglyceride	164.74 ± 80.94	< 150 mg/dl
INR ^c	1.44 ± 2.26	2-3

^a HDL: High Density Lipoprotein.^b LDL: Low Density Lipoprotein.^c INR: International Normalized Ratio.

3.7. Post discharge medications

The most important result in our study is the post discharge medication adherence, 73 % of the patients were on antithrombotic, 47.5 % on antihypertensive and 40.7 % on lipid lowering agents. On the other hand 30.4 % of the patients had a combination of all the three drugs (Table 7).

3.8. Correlation between hospital setting and post discharge adherence

The results show that public hospitals adhere more than private ones with the guidelines for post-discharge medications 48.1 % versus 22.6 % respectively and with a significant p-value of 0.055. The results support non-significant finding that university hospitals adhere with

Table 6
Blood pressure difference post treatment.

Difference of blood pressure	Mean ± standard deviation (mmHg)	P value
Difference of systolic blood pressure between baseline and after 2 hours	6.44 ± 22.11	0.019
Difference of systolic blood pressure between baseline and after 24 hours	25.18 ± 33.45	< 0.001
Difference of diastolic blood pressure between baseline and after 2 h	0	0.159
Difference of diastolic blood pressure between baseline and after 24 h	12.71 ± 13.63	< 0.001

Table 7
Post discharge prescription medications.

Medications	Frequency (n)	Percentage (%)
Antithrombotic	149	73
Antihypertensive	97	47.5
Lipid lowering agents	83	40.7
The three following medications together	62	30.4

Table 8
Correlation between hospital setting and post discharge adherence.

Hospital setting	Post discharge adherence	P value
Private versus public hospital	7 (22.6 %) versus 13 (48.1 %)	0.055
University versus Non university hospital	12 (41.4 %) versus 7 (22.6 %)	0.166

the post discharge medication prescription more than non-university settings with p-value of 0.166 (Table 8).

4. Discussion

This study was a two years retrospective trial investigating the physician adherence to post discharge secondary prevention of stroke guidelines. An assessment of prescribing various post discharge medications such as anti-thrombotic, anti-hypertensive, lipid lowering agents, and measurement of blood pressure at different timeline in the hospital was done using an organized data collection sheet. It was the first study of its kind in Lebanon to date, that assesses the adherence of Lebanese physicians to post discharge medications.

The study had a primary objective, which is to ensure that physicians are prescribing the recommended drugs according to American Heart Association (AHA) guidelines [12], to prevent further stroke attack to decrease mortality and morbidity resulting from recurrent stroke.

4.1. Blood pressure

This study showed significant decrease in mean systolic blood pressure (SBP) from baseline, 2 h, and 24 h after treatment by a mean value of 25.18 ± 33.45 (P < 0.001) and 6.44 ± 22.11 (P = 0.019) respectively. With respect to diastolic blood pressure showed significant decrease only between baseline and after 24 h after treatment by a mean value 12.71 ± 13.63 (P < 0.001).

A study done by Arima H. et al., examined the effect of randomized treatment in 4 subgroups defined by baseline SBP (≥160, 140–159, 120–139, or < 120 mmHg) and the association between achieved BP (same groupings) and risk for recurrent stroke. The first analysis showed that the effectiveness of hypertension therapy for secondary stroke prevention diminished as baseline BP declined and the relative risk ratio was 39 %, 31 %, 14 %, and 0 % respectively, in the groups defined above. This trend of diminishing effect was apparent despite successful reduction of mean systolic blood pressure (SBP) in each active treatment group compared with placebo (11.1, 9.2, 7.6, 7.4 mm Hg reductions respectively in the groups defined above). But this study

concluded that no patient group among whom more intensive BP lowering would not be expected to produce greater risk reductions [14].

In another study done by Castilo J. et al., discussing blood pressure decrease during the acute phase of ischemic stroke and the association with brain injury and poor stroke outcome showed that SBP during the first day was lower than SBP on admission in 233 patients. The mean absolute decrease was 8 ± 7 mmHg in patients who did not receive antihypertensive treatment after admission ($n = 166$) and 36 ± 22 mmHg in those who were treated with anti-hypertensive drugs ($n = 67$) ($P < 0.001$). Similarly, diastolic blood pressure (DBP) decreased in 249 patients during the first 24 h, with the mean value being higher in those who received treatment (23 ± 12 versus 8 ± 7 mmHg; $P < 0.001$). This study also concluded that high and low SBP and DBP, as well as a relevant drop in BP, are associated with poor prognosis in patients with ischemic stroke [15].

4.2. Anti-hypertensive drugs

For anti-hypertensive drugs, 47.5 % of the admitted patients in this study that was admitted to the hospital due to ischemic stroke event were discharged with anti-hypertensive drug. A meta-analysis of randomised trials done by Lisheng L. et al., confirmed that anti-hypertensive medications reduced the risk of recurrent stroke after stroke or TIA. It included 10 randomised trials published through 2009 that compared hypertension therapy with placebo or no therapy. Overall, treatment with anti-hypertensive drugs was associated with a significant reduction in recurrent stroke (RR 0.78, 95 % CI 0.68-0.9) [16].

In another retrospective study done by Lee H. et al., indicated that among 3852 patients with hypertension 957 (2.5 %) had also stroke that occurred during this study period. Non-adherence to medication was significantly associated with a higher risk of stroke (intermediate adherence: adjusted relative risk (aRR) = 1.13, 95 % CI 1.06-1.21), and poor adherence aRR = 1.27, 95 % CI 1.13-1.38) [17].

Moreover, study done by Mugwano I. et al., discussing poor drug adherence and lack of awareness of hypertension among hypertensive stroke patients in Kampala, Uganda showed that out of 112 hypertensive subjects with stroke that were enrolled between May 2013 and April 2014, 70 % had ischemic strokes. Only 17 % were adherent to anti-hypertensive medications [18].

4.3. Anti-thrombotic agents

In this study 73 % of patients were discharged on anti-thrombotic agents. Mainly four antiplatelet drugs have been approved by the FDA for prevention of vascular events among patients with a stroke or TIA (aspirin, combination aspirin/dipyridamide, clopidogrel, and ticlopidine). On average according to a study done by Baigent C, et al. these agents reduce the relative risk (RR) of stroke, myocardial infarction (MI) or death by 22 %, this result was documented in a meta-analysis of randomised trials of antiplatelet therapy for prevention of death, MI, and stroke [19].

Moreover, in a meta-regression analysis of placebo-controlled trials of aspirin therapy for secondary stroke prevention done by Johnson E. et al., the RR reduction for any type of stroke was estimated at 15 % (95 % CI, 6 %-23 %) [20]. While in multi-center observational study done by Kim W. Et al, in Korea studying the adherence to guidelines for anti-thrombotic therapy in patient with atrial fibrillation (AF) according to CHADS2 score before and after stroke. This study was done over 12-month period enrolling 562 in-patients for acute ischemic stroke and with AF in Korea, this study showed that 50 % of the patients had not received any anti-thrombotic drug therapy when they experienced a stroke, and 11 % of the patients did not receive any anti-thrombotic agents at discharge [21].

In another study done by Hills N. et al., in US hospitals was studying the trends in usage of alternative anti-platelet therapy after stroke and

TIA. This study enrolled 18,020 in-patients with ischemic stroke or TIA, it was concluded that only 89 % of the patients were discharged on anti-thrombotic medications [22].

4.4. Lipid lowering agents

With respect to lipid lowering agents, a study done by Chaturvedi S. et al., showed 40.7 % of the patients were discharged with lipid lowering agents. Based on a study published in 2007 stated that patients with a mean LDL-C ≥ 100 mg/dl had a significantly increased risk of recurrent stroke compared to patients with mean LDL-C < 100 mg/dl ($P = 0.03$) [23].

Furthermore, a study done by Saposnik G. et al., enrolled 913,436 patients with an acute ischemic stroke or TIA. Only 194,557 (21.3 %) had previous stroke/TIA, from those only 68 % of patients were at their preadmission National Cholesterol Education Program III guideline-recommended LDL target, 51.3 % had LDL < 100 mg/dl, and only 19.8 % had LDL < 70 mg/dl [24].

In cohort study done by Chen P. et al., in Taiwan, among 193,902 patients with ischemic stroke or TIA, 15,408 patients had statin therapy initiated during hospitalization or within 3 months after discharge [25]. Another study done by Chen P. et al., discussed the impact of early statin therapy in patients with ischemic stroke or TIA. The study endpoint was the composite outcome of ischemic stroke, TIA, haemorrhagic stroke, or acute coronary event. As compared with in hospital use, patients with late use had a 49 % increased stroke risk (adjusted hazard ratio = 1.49, 95 % CI 1.26-1.76). This highlights the fact that in acute ischemic stroke, patients receiving late statin treatment carried a poorer clinical outcome than those with earlier statin initiation [26].

Most of the studies done were on patient instead of physician adherence. Also the majority of the studies were discussing every medication adherence alone post discharge. To our knowledge there were no studies that assessed the physician adherence to the three medications at time.

There are many reasons that can be raised as assumptions for the lack of physician adherence to the secondary stroke prevention guidelines, which is the lack of adoption of the guidelines among the Lebanese hospitals, incomplete patient profile for the past medical history and laboratory results, and avoidance of drug prescription due to the fear from polypharmacy in stroke patients who are mainly elderly.

4.5. Limitations and strengths

The major limitation of this study was its retrospective nature which can lead to some data might be missed as the prescribed medications post discharge which could have been used in the study. Another limitation was lack of hospital randomization since the researchers didn't have access to most hospitals due to the time needed to get an Institutional Review Boards approval; this may limit the sample and its external validity. This trial is the first of its kind in Lebanon that evaluates the adherence of Lebanese physicians post discharge medications. The study is multi-center conducted in different hospitals in Lebanon and from various regions including Beirut and South. Moreover, the data collection sheet used is structured and facilitates the collection of different kinds of information. Also, a statistician supervised all data entry and analysis.

The inappropriate prescriptions of post discharge medications contribute to increase in the risk of secondary stroke occurrence. In our hospitals the inappropriate physician adherence to secondary prevention of stroke guidelines may have an important impact on patients' quality of life. The findings of this study revealed that inappropriate adherence to post discharge medications should be taken into consideration in Lebanese hospitals. Thus, educational programs and some standard form of prescription, and adherence to guideline protocols should be prepared and generalized to the hospitals. Adherence to the

guideline could minimize the long term consequences of stroke and decrease risk of reoccurrence. Further studies incorporating a larger sample size on a longer duration and covering a wider number of Lebanese hospitals in different regions besides Beirut, will help to further generalize the results and effectively identify other risk factors that may increase risk of recurrence of stroke.

Author contributions

DM, SC and SS were responsible for the data collection and entry. DM, HH and PS designed the study; DM drafted the manuscript; DM, SH and PS carried out the analysis and interpreted the results; SH assisted in drafting and reviewing the manuscript; all authors reviewed the final manuscript and gave their consent; HH and PS were the project supervisors.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix D: Data Collection Sheet

Assessment of acute stroke treatment, hypertension, and post discharge medication prescription among Lebanese patients with ischemic stroke: Results of a cross-sectional study

Patient's Demographics:

1. Patient Number: ____, Patient Age: ____, Physician Name: _____, Patient phone number: _____
2. Gender : Male Female
3. Weight: _____Height: _____BMI: _____
4. BMI categories: Normal Overweight Obese Missing data
5. Marital status: Married Single Divorced/widow
6. Work status: Works Jobless Retired Unknown
7. Dwelling region: Beirut Mount Lebanon Bekaa North Lebanon South Lebanon
 Nabatieh
8. Current Smoking: Yes No Not documented
Number of smoked cigarettes per day: _____
Duration of smoking cigarettes: _____
9. Daily Alcohol Consumption: Yes No Not documented
Number of alcohol cups consumed per day: _____
Duration of alcohol intake: _____
10. Watpipe smoking: Yes No Not documented
Number of smoked watpipe per day: _____ Duration of smoking watpipe: _____

11. Hospital setting: Private Public

12. University hospital: Yes No

13. Vascular risk factors:

<i>Disease</i>	<i>Yes</i>	<i>No</i>	<i>Not documented</i>
Hypertension			
Stroke			
TIA			
Arrhythmias			
Hyperlipidemia			
Diabetes			
Dementia or cognitive impairment			
Myocardial infarction			
Congestive heart failure			
Angina			
PCI			
CABG			
Migraine			
No physical activity			
Peripheral artery disease			
Family stroke history			
Family heart disease history			

14. Was the patient previously on Unfractionated Heparin?

Yes No Unknown Contraindicated

15. Was the patient previously on Low Molecular Weight Heparin?

Yes No Unknown Contraindicated

16. Was the patient previously on Vitamin K antagonist?

Yes No Unknown Contraindicated

17. Was the patient previously on antiplatelet therapy?

Yes, Specify drug, dose, duration: _____

No

Unknown

Contraindicated

18. Was the patient previously on lipid-lowering treatment?

Yes, specify: _____

No

Unknown

Contraindicated

19. Was the patient prescribed previously anti-hypertensives?

None

One drug

- Two drugs
- More than three drugs
- Missing data

20. Antihypertensive drug in use at baseline:

- ARB
- ACE inhibitor
- CCB
- Beta blocker
- Alpha blocker
- Unknown

21. Baseline Lab values of:

- blood glucose level: _____
- systolic blood pressure: _____
- diastolic blood pressure: _____
- total cholesterol level: _____
- LDL level: _____
- HDL level: _____
- TG level: _____
- INR level: _____

Hypertension History:

1. Hypertension:

- Diagnosis at admission: Yes No Not documented
- Currently used antihypertensive drugs (within 30 days before study): Yes No Not documented
- Ceased using anti-hypertensive drugs (within 30 days before study): Yes No Not documented

Blood pressure readings:

Blood Pressure Readings at baseline	Blood Pressure Readings 2 hours after thrombolysis	Blood Pressure Readings 24 hours after thrombolysis

2. Is the patient eligible for acute reperfusion? Yes No

If the pateint is eligible for reperfusion:

Is the pateint BP>185/110 mm Hg? Yes No

Was Labetalol administered? Yes No

Was it given in the corect dose (10 - 20mg)? Yes No

Was it given for the correct duration (over 1–2 minutes)? Yes No

Was it repeated in the correct frequency (1 time)? Yes No

Was Nicardipine administered? Yes No

Was it given in the correct dose (5mg/hour IV)? Yes No

Was it given for the correct titration (2.5 mg/h q 5-15 minutes)? Yes No

Other drugs administered: _____

3. If the patient is not eligible for acute reperfusion therapy:

Was the SBP > 220 mm Hg or DBP of 121–140 mm Hg? Yes No

Which drug was administered? labetalol IV nicardipine IV infusion

Was there a reduction of 10%–15% in BP? Yes No

Was the DBP >140 mm Hg? Yes No

Was IV sodium nitroprusside administered? Yes No

Was there a reduction of 10%–15% in BP? Yes No

Stroke History:

1. Stroke onset when: Awake Asleep

2. Consciousness level: Unconscious Drowsy Alert

3. Did the patient have a brain scan after the stroke? Yes No

4. Ischemic stroke subtype:

Thrombotic Embolic Lacunar

5. Did the patient receive intravenous thrombolysis (rt-PA)? Yes No Unkown

6. Did the pateint receive rt-PA within 4.5 hours? Yes No Unkown

7. Time from symptom onset to rt-PA administration: _____

8. Time of stroke onset:

Known time of onset

If uncertain time of stroke, then time last seen well

If wake up stroke, then time last seen well

Time unknown

9. Time from door to rt-PA administration: _____

10. Was there a serious adverse event related to thrombolysis? Yes No

Type of adverse event

Intracranial hemorrhage: Yes No

Extracranial hemorrhage: Yes No

Angioedema: Yes No

Other: Yes No

11. Occlusion sites:

Internal carotid artery (ICA)

Middle cerebral artery M1 segment (MCA M1)

Middle cerebral artery M2 segment (MCA M2)

Anterior cerebral artery

Tandem occlusion corresponding to the artery occlusion occurring in > 2 different parts of continuous vessels

12. Stroke etiology:

Large atherosclerosis

Cardioembolism

Others /undetermined

13. Modified Rankin Scales:

At baseline:

0 - No symptoms.

1 - No important disability

2 - Light disability

3 - Moderate disability

4 - Moderately severe disability

5 - Severe disability

6 - Death

At discharge:

0 - No symptoms.

1 - No important disability

2 - Light disability

3 - Moderate disability

4 - Moderately severe disability

5 - Severe disability

6- Death

14. Hospital inpatient length of stay: _____
15. In-hospital deaths: _____, Out hospital deaths rate: _____
16. Grades of hemorrhagic transformation: _____
17. Symptomatic intracranial hemorrhage (sICH) after rt-PA administration: _____

Assessment of guidelines adherence:

Emergency treatment:

1. Was the brain imaging performed within 20 minutes upon hospital admission?
 Yes No
2. Is the patient candidate for IV alteplase therapy? Yes No
If yes, is the BP lowered to systolic BP <185 mmHg and diastolic BP is <110 mmHg before IV fibrinolytic therapy is initiated? Yes No
3. Is the patient temperature >38 °C? Yes No
If yes, Is antipyretic medication administered to lower temperature in patients with stroke?
 Yes No
4. Is the patient blood glucose >180 mg/dL? Yes No
If yes, is hyperglycemia treated to achieve blood glucose level of 140-180 mg/dL?
Yes No

Aspirin:

5. Is Aspirin administered within 24 to 48 hours after stroke onset? Yes No

6. Is Aspirin administration delayed until 24 hours later after IV alteplase administration?
 Yes No

Anticoagulants:

7. Is anticoagulant administered? Yes No

If yes, choose: LMWH Heparin Argatroban Dabigatran

In-Hospital Management:

1. Was the brain imaging performed within 20 minutes upon hospital admission?
 Yes No

2. Is the antihypertensive given 48 - 72 hours in patients with BP \geq 220/120 mmHg who did not receive IV alteplase and have no comorbid conditions? Yes No

3. Is the patient temperature >38 °C? Yes No

If yes, Is antipyretic medication administered to lower temperature in patients with stroke?
 Yes No

4. Is the patient blood glucose >180 mg/dL? Yes No

If yes, is hyperglycemia treated to achieve blood glucose level of 140-180 mg/dL?
Yes No

Anticoagulants:

5. Is intermittent pneumatic compression applied to the patient? Yes No

6. Is anticoagulant administered? Yes No

If yes, choose:

LMWH Heparin Argatroban Dabigatran

7. Is the structured depression inventory administered to screen for poststroke depression?

Yes No

Discharge:

On discharge was the patient prescribed anti-thrombotics?

Yes No Unknown Contraindicated

On discharge was the patient prescribed anti-hypertensives?

Yes No Unknown Contraindicated

On discharge was the patient prescribed lipid-lowering treatment?

Yes No Unknown Contraindicated