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THESE EN COTUTELLE

Pour obtenir le grade de Docteur délivré par

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Ecole Doctorale des Sciences de la Vie et de la Santé

Mention: Biologie Cellulaire et Moléculaire

Spécialité: Pharmacologie et Biothérapies

Et

L'Université Libanaise

Ecole Doctorale des Sciences et Technologie

Spécialité: Recherche Cliniques

Présentée par

ABDO Rachel

**ETUDE MEDICO-ECONOMIQUE DE LA PRISE EN CHARGE DES ACCIDENTS VASCULAIRES
CEREBRAUX AU LIBAN**

Coûts de la maladie, Mortalité, Qualité de vie

Dirigée par

Directeurs: SALAMEH Pascale - HOSSEINI Hassan

Soutenue le 17 Décembre 2018

Membres du Jury:

MAZIGHI Mikael	Professeur à l'Université Denis Diderot Paris 7	Rapporteur
MAARAWI Joseph	Professeur à l'Université Saint Joseph	Rapporteur
BERDEAUX Alain	Professeur à l'Université Paris Est	Examineur
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HOSSEINI Hassan	Professeur à l'Université Paris Est	Directeur
SALAMEH Pascale	Professeur à l'Université Libanaise	Directeur

DEDICATES

I dedicate this thesis work to my dear parents.

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ABSTRACT

Stroke is a disease with high morbidity and mortality rates, classified among the most common causes of death and acquired disability worldwide. Thus, assessing its epidemiology may play a crucial role in reducing its impact on the population and the society. Stroke late burden is attributable to developing countries mainly, as people in developed countries have a better access to optimal care and an increased awareness on stroke symptoms and risk factors. However, in less developed countries, where population confronts the huge impact of urbanization and globalization with a great increase in the prevalence of cardiovascular risk factors, the incidence of stroke remains high. Lebanon is lacking data on the epidemiology of stroke. Therefore, it was necessary to conduct this study and highlight some features of the disease epidemiology.

We carried out a multicenter prospective incidence-based cohort study. We included 203 participants aged 18 years and more from 8 hospitals in Beirut between August 2015 and August 2016 with confirmed diagnosis of stroke. Patients were followed for a 1-year period (at hospital admission and discharge, and by home visits at 3, 6 and 12 months).

Hypertension was the most powerful and prevalent risk factor for stroke. Only 2.5% of ischemic strokes received thrombolytic therapy. Cumulative mortality rates were 13.3% at 1-month and 21.2% at 1-year. Stroke severity and complications were predictors of death at 1-month and 1-year. Low socioeconomic status, dependency in daily living activities, and comorbidities were additional 1-year mortality predictors. The quality of life was relatively low in stroke patients and more than 15% of them were depressed. The main determinants of quality of life were functional status, dependency in daily living activities, age, and depression. The main determinants of depression were functional status and quality of life. The direct in-hospital cost for all cases was US\$1,413,069 for 2626 days (US\$538 per in-hospital day). The average in-hospital cost per stroke patient was US\$6961±15,663. Hemorrhagic strokes were the most costly, transient ischemic attack being the least costly. Cost drivers were hospital and intensive care unit length of stay, type of stroke, stroke severity, modified Rankin Scale, third party payer, surgery and infectious complications.

Primary prevention is of paramount importance in reducing the burden of stroke. Awareness campaigns on stroke symptoms especially among hypertensive population would help limit the incidence of the disease and therefore decrease the high financial and social burden of stroke (cost of illness and quality of life). The establishment of stroke units and increasing the percentage of thrombolysis may reduce short-term mortality and long term disabilities and therefore improve the quality of life of stroke patients.

KEYWORDS

STROKE; LEBANON; QUALITY OF LIFE; COST OF STROKE; TRANSIT ISQUEMIC ATTACK;
MORTALITY; MANAGEMENT.

RESUME

L'accident vasculaire cérébral (AVC) est une maladie avec des taux de morbidité et de mortalité élevés, il est classé parmi les causes les plus fréquentes de décès et d'invalidité acquise dans le monde entier. Ainsi, évaluer son épidémiologie peut jouer un rôle crucial dans la réduction de son impact sur la population et la société. Le fardeau de l'AVC est attribué principalement aux pays en voie de développement, puisque les gens dans les pays développés ont une meilleure prise en charge et une sensibilisation accrue sur les symptômes et les facteurs de risque de l'AVC. Toutefois, dans les pays moins développés, où la population confronte l'énorme impact de l'urbanisation et de la mondialisation avec une augmentation accrue de la prévalence des facteurs de risque cardiovasculaire, l'incidence des AVC reste élevée. Peu de données épidémiologiques existent sur les AVC au Liban. Par conséquent, il était nécessaire de mener cette étude.

Nous avons effectué une étude de cohorte multicentrique, prospective, basé sur l'incidence. Nous avons inclus 203 participants âgés de 18 ans et plus de 8 hôpitaux à Beyrouth entre Août 2015 et Août 2016 avec un diagnostic d'AVC confirmé. Les patients ont été suivis pendant une période d'un an (à l'admission à l'hôpital, à la sortie de l'hôpital et à 3, 6 et 12 mois par des visites à domicile).

L'hypertension est le facteur de risque le plus puissant et le plus fréquent de l'AVC. Seulement 2,5 % des AVC ischémiques ont subi une thrombolyse. Le taux de mortalité cumulé était 13,3% à 1 mois et 21,2% à 1 an. Les complications et la gravité de l'AVC étaient des prédicteurs de décès à 1 mois et 1 an. Le niveau socio-économique bas, la dépendance dans les activités quotidiennes et les comorbidités étaient prédicteurs de mortalité supplémentaire à 1 an. La qualité de vie est relativement faible chez les patients atteints d'AVC et plus de 15 % d'entre eux étaient déprimés. Les principaux déterminants de la qualité de vie étaient: l'état fonctionnel, la dépendance dans les activités de la vie quotidienne, l'âge et la dépression. Les principaux déterminants de la dépression étaient l'état fonctionnel et la qualité de vie. Le coût direct hospitalier de tous les cas d'AVC était US\$ 1,413,069 pour 2626 jours (538 US\$ par jour à l'hôpital). Le coût moyen hospitalier par patient était US\$ 6961±15, 663. Les AVC hémorragiques ont été les plus coûteux, l'accident ischémique transitoire étant le moins coûteux. Les prédicteurs de coûts étaient : la longueur du séjour hospitalier et dans l'unité de soins intensifs, le type d'AVC, la gravité de l'AVC, l'échelle de Rankin modifiée, les tiers payeurs, la chirurgie et les complications infectieuses.

La prévention primaire est d'une importance primordiale dans la réduction de la charge de l'AVC. Les campagnes de sensibilisation sur les symptômes de cette maladie surtout pour la population hypertendue contribueront à limiter l'incidence de la maladie et donc à diminuer le fardeau financier et social élevé de l'AVC (le coût de la maladie et la qualité de vie). La mise en place d'unités spécialisées pour les AVC et l'augmentation du pourcentage de patients thrombolysés peuvent réduire la mortalité à court terme et les incapacités de longue durée et donc améliorer la qualité de vie des patients atteints d'AVC.

MOTS CLES

ACCIDENTS VASCULAIRES CEREBRAUX; LIBAN; QUALITE DE VIE; COUT DE LA MALADIE;
ACCIDENT ISCHEMIQUE TRANSITOIRE; MORTALITE; MANAGEMENT.

LABORATORY

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RESUME SUBSTANTIEL

INTRODUCTION

I- DEFINITION ET TYPES

Les accidents vasculaires cérébraux (AVC) font partie d'un groupe de maladies chroniques appelées les maladies cardiovasculaires (MCV). L'Organisation Mondiale de la Santé (OMS) définit un AVC comme « le développement rapide de signes cliniques localisés ou globaux de déficit ou dysfonction cérébrale avec des symptômes durant plus de 24 heures pouvant conduire à la mort, sans autre cause apparente qu'une origine vasculaire » (WHO MONICA Project Investigators, 1988). Les AVC se caractérisent par leur grande diversité et la forte invalidité qu'ils peuvent engendrer à long terme. Ils recouvrent un ensemble de syndromes se manifestant par l'apparition brutale d'un déficit neurologique dû à des lésions cérébrales d'origine vasculaire.

On distingue:

- Les Accidents Ischémiques:
 - ✓ Transitoires (AIT): un AIT est un déficit neurologique focal, d'installation brutale, et entièrement régressif et sans signe d'infarctus constitué à l'imagerie cérébrale.
 - ✓ Constitués: un AVC constitué est un déficit neurologique de topographie vasculaire durable, consécutif, le plus souvent, à l'occlusion d'une artère cérébrale.
- Les Accidents Hémorragiques:
 - ✓ Sous-arachnoïdiens ou méningés dus à la rupture des anévrismes artériels du polygone de Willis (dans l'espace sous-arachnoïdien).
 - ✓ Cérébro-méningés dus à la rupture des malformations artério-veineuses.
 - ✓ Cérébraux ou intraparenchymateux dus à la rupture des microanévrismes de Charcot et Bouchard situés sur les artéριοles perforantes (c'est dans ce dernier cas qu'on parle d'AVC hémorragique).

En moyenne, 87% des AVC sont ischémiques. Ces derniers résultent le plus souvent d'une occlusion vasculaire dont les 2 principaux mécanismes sont la thrombose et l'embolie. L'embolie peut avoir comme point de départ soit le cœur soit une plaque d'athérome qui est à l'origine aussi des thromboses (occlusion complète de l'artère) (AHA/ASA; 2018).

La classification TOAST (Adams et al., 1999):

- Les athéroscléroses des gros vaisseaux
- La cardiopathie emboligène
- Les maladies des petits vaisseaux ou lacunes
- Autres causes (notamment des troubles hématologiques)
- Les AVC de cause indéterminée (dans le cas où l'évaluation est incomplète ou négative, ou s'il y a plus d'une cause identifiée)

II- FACTEURS DE RISQUE DES AVC

FACTEURS DE RISQUE MODIFIABLES

Hypertension artérielle (HTA): La relation entre la tension artérielle et le risque d'AVC est étiologiquement et fortement significative, rendant l'HTA le premier facteur de risque de l'AVC ischémique et hémorragique. En effet, le risque d'AVC attribuable à l'hypertension atteint 35% pour tous les types d'AVC (O'Donnell et al., 2010).

Tabagisme: Le tabagisme (cigarettes, cigares, pipes et nargileh) actif ou passif est un facteur de risque indépendant de l'AVC ischémique et de l'hémorragie sous-arachnoïdienne et en un moindre degré de l'hémorragie intracérébrale. Les fumeurs actuels ont un risque d'AVC 2 à 4 fois plus élevé que les non-fumeurs ou ceux qui ont cessé de fumer depuis plus de 10 ans (Meschia et al., 2014).

Diabète mellitus: Les diabétiques sont 2 fois plus à risque de subir un AVC que les personnes non diabétiques, ce risque concernant les AVC ischémiques beaucoup plus que les AVC hémorragiques (O'Donnell et al., 2010).

Régime alimentaire: Les études épidémiologiques ont mis en évidence un effet protecteur d'un régime alimentaire pauvre en sel et riche en fruits et légumes ainsi qu'un régime alimentaire Méditerranéen sur l'incidence d'un AVC (Estruch et al., 2013; Larsson et al., 2013).

Manque d'activité physique: L'inactivité physique augmente le risque d'AVC (Willey et al., 2017). Une activité physique régulière était associée à un risque réduit d'AVC (O'Donnell et al., 2010).

Surpoids et obésité: Le surpoids et l'obésité sont des facteurs de risque majeurs de maladies cardiovasculaires, y compris les AVC (Goldstein et al., 2011).

Dyslipidémie: Les études épidémiologiques montrent que le taux de cholestérol total (surtout le LDL) est plus ou moins corrélé à l'incidence d'un AVC: Pour des taux plus élevés, l'incidence d'un AVC ischémique augmente (Kurth et al., 2007) alors que celle d'un AVC hémorragique diminue (Sturgeon et al., 2007).

Fibrillation auriculaire (FA): La FA (paroxystique ou chronique) multiplie le risque d'AVC cardioembolique par un chiffre allant de 4 à 5 (Turakhia et al., 2015). De plus, la FA est la source cardiaque de thromboembolie la plus fréquente dans les cas des AVC ischémiques (O'Donnell et al., 2010).

Autres troubles cardiaques: Infarctus du myocarde, maladies valvulaires

Syndrome métabolique: Le syndrome métabolique est associée à un risque plus élevé d'AVC (Mottilo et al., 2010).

Maladie rénale chronique: Une méta-analyse a montré une augmentation de 43% du risque d'AVC chez les patients présentant un DFG $<60 \text{ mL.m}^{-1},73 \text{ m}^{-2}$ (Lee et al., 2010).

L'apnée du sommeil: Le risque d'AVC ischémique et hémorragique est plus élevé avec l'apnée du sommeil. Dans une méta-analyse de 5 études, l'apnée obstructive du sommeil est associée à l'AVC, avec un OR de 2,2 (IC à 95%, 1,6–3,2) (Loke et al., 2012).

Alcoolisme: Le risque d'AVC est augmenté avec la consommation excessive d'alcool. La plupart des études montrent une association en forme de J entre le nombre de verres consommés par jour et le risque d'AVC ischémique: La consommation légère à modérée d'alcool aurait un effet protecteur contre le risque d'AVC ischémique mais non pas hémorragique (O'Donnell et al., 2010).

Abus de drogues: Le risque d'AVC ischémique et hémorragique est plus élevé avec l'abus de ces drogues (AHA/ASA).

Habitudes de sommeil: Des études récentes ont commencé à clarifier les raisons pour lesquelles les personnes qui dorment régulièrement et de bonne qualité tendent à présenter moins de risques d'AVC (AHA/ASA). Dans une méta-analyse récente de 10 études, une relation

en forme de J a été rapportée entre la durée du sommeil et le risque d'AVC, le risque le plus faible étant observé chez les personnes ayant une durée de sommeil de 6 à 7 heures par jour (Li et al., 2016).

FACTEURS DE RISQUE NON MODIFIABLES

Age: L'âge augmente le risque d'AVC par ses effets cumulatifs sur le système cardiovasculaire. Les personnes sont plus susceptibles d'avoir un AVC après l'âge de 55 ans (Wang et al., 2013). La probabilité d'avoir un AVC double presque tous les 10 ans après l'âge de 55 ans (Rothwell et al., 2005).

Facteurs génétiques: Des études génétiques ont identifié des variantes génétiques associés à un risque d'ischémie cérébrale (Flossmann et al., 2004) et d'ICH (Chauhan and Debette, 2016). Une histoire familiale d'AVC augmente le risque d'AVC de 25% (Seshadri et al., 2010).

Race: Les statistiques montrent que les Afro-Américains (Hispaniques) ont un risque beaucoup plus élevé de décès par AVC que les Caucasiens (White et al., 2005). Le risque d'avoir un premier AVC est de deux fois plus élevé pour les Noirs que pour les Blancs (Benjamin et al., 2017) et les Noirs ont le taux de décès par AVC le plus élevé (Vital Signs, 2017).

Sexe: Les femmes sont significativement plus âgées lors de leur tout premier AVC, et ont une incidence d'AVC supérieure à 85 ans, et inférieure à tous les autres âges (Haast et al., 2012). Le risque d'AVC est augmenté de 9% par année d'âge chez les hommes et de 10% chez les femmes (95% IC= 9-10%) (Asplund et al., 2009). Les femmes ménopausées sont plus à risque que les non-ménopausées de développer un AVC (Boardman et al., 2015).

Le statut socio-économique: L'éducation, le revenu et l'occupation sont les 3 principaux déterminants du statut socioéconomique. Les études ont montré une association négative entre le risque d'AVC et le statut socioéconomique (CDC, 2012).

III- PRISE EN CHARGE PRECOCE DES AVC

PHASE PRE-HOSPITALIERE ET EVALUATION DU PATIENT:

Suspecter un AVC / Echelle FAST:

La reconnaissance des symptômes devant faire évoquer un AVC ou AIT est primordial auprès des acteurs du premier secours (membres de famille, ambulanciers, secouristes, médecins généralistes, etc.). Dans ce but, un outil simple et rapide est utilisé en général pour ne pas s'attarder à offrir la prise en charge nécessaire aux patients d'AVC. Cet outil est le test FAST:

- ✓ F pour Face: perte de force ou engourdissement du visage.
- ✓ A pour Arm: perte de force ou engourdissement au niveau d'un membre supérieur.
- ✓ S pour Speech: trouble de la parole.
- ✓ T pour Time: pour agir le plus rapidement possible.

Plusieurs pays, tels que le Royaume-Uni et la France, ont lancé des campagnes nationales de sensibilisation de la population aux symptômes des AVC: les campagnes "Act FAST" (Powers et al., 2018).

Les patients présentant un dépistage positif de l'AVC et/ou une forte suspicion d'AVC devraient être transportés rapidement vers les établissements de santé les plus proches capables d'administrer de manière compétente l'altéplase IV (Classe I, LOE B) (Powers et al., 2018).

PHASE HOSPITALIERE

Evaluer la sévérité de l'AVC / Echelle NIHSS:

Le NIHSS est le plus couramment utilisé. Il est composé de 11 questions qui marquent chacune une capacité neurologique spécifique et dont les réponses prennent un score allant de 0 (réponse normale) à 2, 3 ou 4 (dysfonctionnement sévère). Les scores individuels de chaque élément sont additionnés pour donner le score total NIHSS. Les questions portent sur le niveau de conscience, la vision, la paralysie faciale, la motricité et l'ataxie des membres, la sensibilité, le langage, l'extinction et la négligence.

Le score total prend un chiffre allant de 0 à 42:

- ✓ Un score de 1 à 4 indique un AVC mineur.
- ✓ Un score de 5 à 15 indique un AVC modéré.
- ✓ Un score de 16 à 20 indique un AVC modéré à sévère.
- ✓ Un score de 21 à 42 indique un AVC sévère.

Il est important d'évaluer la sévérité de l'AVC le plus tôt possible après le début des symptômes pour instaurer le traitement le plus adéquat (notamment décider si le patient est candidat d'une thrombolyse) et pour juger de l'efficacité de ce dernier et des mesures de réhabilitation instaurées plus tard au patient (NIHSS diminue ou augmente). De plus, le NIHSS permet de prédire l'état du patient après AVC: Un score ≤ 6 prévoit un bon pronostic alors qu'un score ≥ 16 prévoit une forte probabilité de décès ou de handicap sévère (Adams et al., 1999).

IMAGERIE CEREBRALE ET VASCULAIRE

Idéalement, l'imagerie doit être initiée dans un délai maximal de 25min depuis l'arrivée du patient à l'hôpital et interprétée dans un délai de 45min ("Door to Imaging initiation" ≤ 25 min; "Door to Imaging interpretation" ≤ 45 min). La neuro-imagerie rapide avec CT scanner ou IRM est recommandée pour distinguer l'AVC ischémique de l'AVC hémorragique. L'IRM (imagerie par résonance magnétique) est l'examen le plus performant pour montrer précocement des signes d'ischémie récente, et elle visualise l'hémorragie intracrânienne. Le CT scanner est très sensible pour identifier une hémorragie aiguë et est considéré comme le «gold standard».

LE TRAITEMENT DES AVC ISCHEMIQUES

LA THROMBOLYSE INTRAVEINEUSE (IV)

La thrombolyse IV par l'altéplase est le traitement de choix (Gold Standard) des AVC ischémiques aigus. L'activateur tissulaire du plasminogène recombinant (rtPA ou altéplase) a été approuvé en 1996 par l'agence Américaine des produits alimentaires et médicaux (FDA) pour le traitement des AVC ischémiques aigus. Cependant, ce traitement ne peut se faire que dans les 3 à 4.5h qui suivent le début des symptômes. Idéalement, le traitement doit être initié dans les 60min suivant l'admission du patient à l'hôpital ("Door to needle" ≤ 60 min).

Dose: 0.9mg/kg (dose maximale 90mg); 10% de la dose en bolus IV et 90% en infusion/ 1h (Powers et al., 2018).

LES INTERVENTIONS ENDOVASCULAIRES

- La thrombolyse intra-artérielle (IA): peut être utilisée au cas par cas si la thrombolyse IV n'est pas possible, après concertation entre neurologues vasculaires et neuroradiologues, et ce jusqu'à 6 heures pour les occlusions de l'artère cérébrale moyenne, voire au-delà de 6 heures pour les occlusions du tronc basilaire du fait de leur gravité extrême (Powers et al., 2018).
- La revascularisation mécanique par thrombectomie ("MERCY Retrieval System", "Penumbra System", "Solitaire Flow Restoration Device", Trevo Retriever") avec ou sans thrombolyse pharmacologique: A évaluer (Powers et al., 2018).

ADMINISTRATION D'ANTIAGREGANTS PLAQUETTAIRES:

- A initier l'aspirine (dose initiale de 325mg) dans les 24-48h suivant le début de l'AVC.
- L'aspirine ne doit pas substituer un traitement éligible par l'altéplase IV.
- L'utilité du clopidogrel dans le traitement des AVC aigus n'est pas bien établie.
- L'administration IV des inhibiteurs du récepteur de la glycoprotéine IIb/IIIa n'est pas recommandée.

TRAITEMENT DES COMPLICATIONS AIGUËS

- L'hypotension et l'hypovolémie doivent être corrigées pour maintenir les niveaux de perfusion systémique nécessaires au soutien de la fonction des organes (Powers et al., 2018).
- Les patients qui ont une tension artérielle élevée et qui sont par ailleurs admissibles à un traitement par rtPA IV doivent voir leur tension artérielle baissée avec précaution de manière à ce que leur pression artérielle systolique soit <185 mm Hg et leur pression artérielle diastolique <110 mm Hg avant le début du traitement par fibrinolytique.
- Les arythmies cardiaques susceptibles de réduire le débit cardiaque doivent être corrigées
- L'hypoglycémie (glycémie <60 mg/dL) doit être traitée chez les patients atteints d'AVC aigu. Le but est d'atteindre la normoglycémie.
- Un supplément d'oxygène doit être fourni chez les patients avec hypoxie pour maintenir la saturation en oxygène >94%.

LE TRAITEMENT DES AVC HEMORRAGIQUES:

Les stratégies thérapeutiques doivent d'abord cibler la cessation de l'élargissement de l'hématome et la prévention des conséquences délétères de l'effet de masse évoqué par l'hémorragie elle-même et l'œdème qui l'entoure. Le développement d'une hydrocéphalie est à surveiller, et des mesures chirurgicales adéquates (Dérivation externe du liquide céphalo-rachidien en cas d'hydrocéphalie aiguë, évacuation d'un hématome cérébelleux compressif, traitement curatif d'une malformation vasculaire, etc.) doivent être prises à temps.

- Mesures antiœdémateuses:
 - ✓ Position semi-assise (30°)
 - ✓ Restriction hydrique
 - ✓ Les corticoïdes sont sans intérêt
 - ✓ Le Mannitol peut être utilisé.
- Traitement des troubles de coagulation:
 - ✓ Arrêt des anticoagulants
 - ✓ Selon le cas: Plasma frais congelé, Concentré plaquettaire (si thrombopénie), sulfate de protamine (si surdosage en héparine), Vitamine K ou concentré de complexe prothrombinique (si surdosage en anti-Vitamine K).
- Gestion du glucose
Le glucose doit être surveillé. L'hyperglycémie et l'hypoglycémie doivent être évitées.
- Traitement des crises convulsives:
Un traitement prophylactique n'est pas recommandé
- Contrôle de la tension artérielle:
 - ✓ Diminution progressive
 - ✓ Maintenir la TAS \leq 140 mm Hg
 - ✓ Nicardipine IV pour les tensions très élevées.

IV- LES AVC EN CHIFFRES

- En 2013, on comptait dans le monde près de 25,7 millions de personnes ayant subi un AVC (71% ischémique), dont 10,3 millions de personnes ayant eu un AVC pour la première fois (Feigin et al., 2015).
- Environ deux sur trois AVC étaient ischémiques (Feigin et al., 2014).
- 5,2 millions (31%) des AVC étaient chez les moins de 65 ans (Feigin et al., 2014).

- En 2013, 10,3 millions de nouveaux AVC (67% ischémique) ont été enregistrés dans le monde (Feigin et al., 2015).
- Les AVC sont la deuxième cause de mortalité la plus fréquente dans le monde après les cardiopathies ischémiques (Donnan et al., 2008; Lozano et al., 2012; Murray et al., 1997; WHO, 2014) avec 6,7 millions de décès en 2012 (environ 12% du total) (WHO, 2014).
- Selon les données de l'OMS, les AVC étaient la troisième cause de perte de DALY dans le monde en 2012. Au total, 113 millions de DALY ont été perdues à la suite d'un AVC en 2013 (Feigin et al., 2015).

QUALITE DE VIE POST-AVC

Plusieurs études ont montré que de loin la plus grande partie des patients éprouvent et signalent une baisse de la qualité de vie après un AVC (Nydevik and Hulter-Asberg, 1992; Williams et al., 1999).

Descriptions génériques des mesures de la qualité de vie

- *Medical Outcomes Short Form Health Survey (SF-36)*
- *Medical Outcomes Short Form Health Survey (SF-12)*
- *Sickness Impact Profile (SIP)*
- *Euroqol*

Mesures de la qualité de vie spécifiques à l'AVC

- *The Stroke Specific Quality of Life Measure (SSQOL)*
- *The Stroke Adapted Sickness Impact Profile (SASIP30)*
- *The Stroke Impact Scale (SIS)*

DEPRESSION POST-AVC

Environ un tiers des victimes d'AVC souffrent de dépression après leur AVC (Ayerbe et al., 2015; Hackett et al., 2005). La dépression post-AVC est associée à une mortalité plus élevée (Bartoli et al., 2013).

SCORES D'EVALUATION DE L'ETAT FONCTIONNEL DU PATIENT APRES AVC

L'AVC cause un plus grand nombre d'incapacités que toute autre condition (Adamson et al., 2004). Environ 3% des hommes et 2% des femmes ont déclaré être handicapés à la suite d'un AVC (CDC, 2009).

Le "Modified Rankin Scale" (mRS)

Le mRS mesure le degré d'indépendance de la personne plutôt que sa performance dans certaines tâches. Il prend un chiffre allant de 0 (pas de symptômes) à 5 (handicap sévère). Le décès est noté 6 sur le mRS. Un résultat "favorable" défini pour des scores mRS ≤ 2 . Le mRS est largement utilisé dans les études cliniques pour évaluer l'efficacité d'un traitement.

Le "Barthel Index" (BI)

Le BI est un score mesurant la performance du patient dans 10 activités de la vie quotidienne: l'alimentation, le bain, la continence rectale, la continence urinaire, les déplacements, les escaliers, l'habillement, les soins personnels, l'usage des toilettes et le transfert du lit au fauteuil. Les catégories de réponse à chaque question prennent un chiffre croissant de 5 en 5, de la dépendance vers l'autonomie. Le score total prend un chiffre allant de 0 (dépendance totale) à 100 (complète autonomie).

COST OF STROKE

Les AVC coûtent aux États-Unis environ 34 milliards de dollars américains chaque année. Ce total comprend le coût des services de santé, des médicaments pour traiter les AVC et des journées de travail manquées (Benjamin et al., 2017). Aux États-Unis, le coût total des AVC en 2010 était estimé à 73,7 milliards de dollars américains par la «US National Stroke Association»; ceci inclut le coût direct des médicaments pour traiter les AVC ainsi que les services de santé, par exemple dans les hôpitaux ou les maisons de retraite, par les médecins, les soins de santé à domicile, etc. (représentant plus de 60% du coût total) et les coûts indirects tels que la perte de productivité (près de 40% du coût total) (National Stroke Association, 2015).

Au Brésil, le coût total moyen de l'hospitalisation initiale était de 4 101±4 254 dollars américains pour les AVC hémorragiques et de 1 902±1 426 dollars américains pour les AVC ischémiques. Les dépenses nationales totales en soins de santé pour le traitement aigu des AVC hémorragique incident s'élevaient à 122,4 millions de dollars américains (fourchette 30,8-274,2) et à 326,9 millions de dollars américains pour les AVC ischémiques (fourchette 82,4-732,2) (Christensen et al., 2009).

En Argentine, le coût total moyen de l'hospitalisation initiale était de 12 285±14 336 dollars américains pour les AVC hémorragiques et de 3 888±4018 dollars américains pour les AVC ischémiques. Les dépenses nationales totales en soins de santé pour le traitement aigu des AVC

hémorragiques incident s'élevaient à 194,2 millions de dollars américains (fourchette 97,1-388,4) et à 239,9 millions de dollars américains pour les AVC ischémiques (fourchette 119,9 à 479,7) (Christensen et al., 2009).

Au Royaume-Uni, une étude publiée en 2009 a tenté d'estimer le coût annuel des AVC pour l'économie du Royaume-Uni (Saka et al., 2009). La recherche a inclus le diagnostic, les soins hospitaliers et les soins ambulatoires dans son estimation des coûts directs; son estimation des coûts indirects comprenait la perte de revenus et le versement de prestations sociales aux survivants d'un AVC. Au total, les recherches ont évalué à 8,9 milliards de livres sterling (12,9 milliards de dollars américains) le coût total du traitement des AVC et de la perte de productivité résultant de ces AVC, les soins directs représentant environ la moitié de ce montant, les coûts des soins informels 27%. et des coûts indirects pour 24%.

En Italie, les coûts sociaux et de soins de santé sur un an s'élevaient respectivement à 11 747€ et 19 953€. Les soins informels représentaient 6 656€ (33,4% du total), suivis de l'hospitalisation initiale (5 573 euros; 27,9% du total), de la rééducation lors du suivi (4 112€, 20,6%), des réadmissions (439€) et les visites de médecins spécialistes et généraux (326€). Le coût moyen des médicaments par patient au cours de la période de suivi était d'environ 50€ par mois. Les coûts liés à la fourniture de services de garde rémunérés et informels ont évolué de manière différente et ont persisté au fil du temps (allant de 639 à 597 € par mois respectivement dans la première et la deuxième partie de l'année) (Fattore et al., 2012).

En Grèce, le coût direct à l'hôpital pour tous les cas d'AVC était de 1 551 445€ pour un total de 4674 jours (332€ par jour à l'hôpital). Le coût moyen à l'hôpital par patient ayant subi un AVC était de 3 625±2 595€. Les AVC hémorragiques étaient beaucoup plus coûteux que les AVC ischémiques (moyenne: 5305±4205€ et 3214±1976, respectivement) et les AVC lacunaires les moins chers parmi les sous-types d'AVC ischémique (Gioldasis et al., 2008).

Dans les 27 pays de l'Union européenne, le coût économique annuel des AVC était estimé à 27 milliards d'euros: 18,5 milliards d'euros (68,5%) pour les coûts directs et 8,5 milliards d'euros (31,5%) pour les coûts indirects. Un montant supplémentaire de 11,1 milliards d'euros a été calculé pour la valeur des soins informels (British Geriatrics Society, 2009). Dans une autre étude de l'Union européenne, le fardeau financier des AVC représentait environ 62 milliards d'euros (70 milliards de dollars américains) par an et représentait environ 2 à 3% de l'ensemble des dépenses de santé de la région (StopAfib, 2012).

En Turquie, le coût moyen des AVC était de 1 677±2964 dollars américains (29,9% des médicaments, 19,9% en laboratoire, 12,8% en neuroimagerie et 38% en lits et en personnel) (Asil et al., 2011).

Au Pakistan, le coût total moyen était de 70 714 roupies (1 117 dollars américains), ce qui comprenait le coût moyen en radiologie; 12 507 roupies (208 dollars américains), coût moyen d'un laboratoire; 8365 roupies (139 dollars américains), coût moyen de la pharmacie; 13 320 roupies (222 dollars américains) et les frais moyens par lit / chambre; 27 552 roupies (459 dollars américains) (Khealani et al., 2003).

Les AVC touchent principalement les individus au sommet de leur vie productive (Walter et al., 2016). Les personnes en âge de travailler qui ont eu un AVC sont deux à trois fois plus susceptibles d'être au chômage huit ans après leur AVC (Maaijwee et al., 2011). Environ 1 survivant d'un AVC sur 6 subit une perte de revenu après un AVC (McKevitt et al., 2011).

SITUATION AU LIBAN

Le Liban est un pays arabe du Moyen-Orient classé parmi les pays à revenu intermédiaire de la tranche supérieure de la région de la Méditerranée orientale (WHO, 2015). Les études disponibles sur les maladies non transmissibles ont montré une prévalence alarmante des facteurs de risque cardiovasculaires tels que l'hypertension artérielle 36% (Matar et al., 2015), le diabète 14% (Tohme et al., 2005), l'obésité 26% (Chamieh et al., 2015), et des facteurs de risque comportementaux tels que le tabagisme (cigarettes 38,5% et pipe à eau 22,4%) (Sibai et Hwalla, 2008) et l'activité physique insuffisante (38%) (WHO, 2015) chez les adultes Libanais. Cependant, les études sur les AVC au Liban sont limitées.

Le taux d'incidence des AVC au Liban n'a pas été étudié jusqu'à présent. Les études montrant la prévalence de l'AVC sont rares et montrent une prévalence variant entre 0,5% et 3,9% (Farah et al., 2015; Jurus et al., 2009; Lahoud et al., 2016).

Un score de risque d'AVC (ROSS) a été mis au point pour dépister les individus à risque d'AVC dans la population Libanaise. Une étude cas-contrôle en milieu hospitalier a été menée pour la génération du score. Un score <2 points indiquait une valeur prédictive négative élevée de l'AVC de 94,4%. Un score >10 points avait une valeur prédictive positive de l'AVC supérieure à 85,4% (El-Hajj et al., 2018a).

Un score de diagnostic d'AVC (DS-stroke) à l'urgence au sein de la population Libanaise à l'aide de facteurs de risque et de symptômes d'AVC a été mis au point pour diagnostiquer les patients atteints d'AVC au service des urgences. Une étude cas-contrôle en milieu hospitalier a été menée pour la génération du score. Un score <4 points indiquait une valeur prédictive négative élevée pour les AVC de 97,3%. Un score ≥ 4 points indiquait une valeur prédictive positive de l'AVC de 91,3% (El-Hajj et al., 2018b).

Une étude épidémiologique nationale a évalué l'association entre la pollution auto-déclarée d'origine intérieure et extérieure et les AVC et les mini-AVC au Liban (Salameh et al., 2018).

Une étude rétrospective a évalué l'existence de mutations génétiques (mutations du gène MTHFR et du facteur V) dans différents types d'AVC chez de jeunes adultes auparavant en bonne santé (Araji et al., 2014).

Une étude rétrospective a analysé la prévalence de tous les AVC hémorragique et ischémique ainsi que les sous-types d'AVC ischémique dans une population de patients hospitalisés dans 2 hôpitaux Libanais. Les sous-types d'AVC ischémique ont ensuite été classés selon la classification TOAST (Trial of Org 10172 dans le traitement de l'AVC aigu) (Adams et al., 1993) et leurs corrélations avec les facteurs de risque d'AVC validés et avec les caractéristiques sociodémographiques de l'échantillon ont été évaluées (Lahoud et al., 2017).

En outre, les AVC sont la deuxième cause de mortalité au Liban après les cardiopathies ischémiques, faisant 2 000 victimes en 2012 (9,4% du nombre total de décès) (OMS, 2015). C'est en outre une des principales causes d'invalidité permanente chez les adultes (OMS, 2015). Cependant, le pays manque d'unités de soins de l'AVC organisées, ce qui rend le statut des soins aigus peu clair et discutable. Ainsi, la situation actuelle dans le pays insiste sur la nécessité de lancer des études épidémiologiques pour évaluer les soins et les conséquences post-AVC (mortalité, handicap, qualité de vie, etc.). Les prédicteurs de décès à l'hôpital peuvent également jouer un rôle majeur dans l'amélioration de la gestion et du pronostic des AVC. Une étude rétrospective en milieu hospitalier a évalué les soins de l'AVC aigu et les résultats à la sortie (Lahoud et al., 2018). Une autre étude rétrospective a examiné les caractéristiques et les résultats des patients, en plus des obstacles à l'utilisation de la thrombolyse dans un centre de soins tertiaires à Beyrouth, au Liban (El Sayed et al., 2014). Une étude réalisée en milieu hospitalier a évalué les avantages et l'impact des interventions thérapeutiques en unité de soins intensifs sur la survie et la capacité fonctionnelle de patients victimes d'un AVC grave (Riachy et al., 2008).

OBJECTIFS

Malgré le fardeau élevé des AVC au Liban, les données nationales épidémiologiques, cliniques et socioéconomiques sur les AVC sont rares et incomplètes, en particulier les études prospectives. Par conséquent, nous avons décidé de mener une étude de cohorte multicentrique prospective medico-économique sur la gestion des AVC au Liban.

Les objectifs de cette thèse étaient:

- D'évaluer les pratiques actuelles des médecins Libanais impliqués dans le traitement des AVC.
- D'évaluer, d'un point de vue sociétal, les coûts financiers et économiques directs hospitaliers de la prise en charge de l'AVC aigu chez les patients hospitalisés atteints d'AVC au Liban (chambre et pension, laboratoire, examens généraux, médecins, médicaments, rééducation, etc.) approche ascendante (analyse cout de la maladie) et évaluer les prédicteurs de coûts.
- Déterminer la qualité de vie des patients victimes d'un AVC un an après l'incidence de l'AVC et ses déterminants.
- Comparer les résultats d'un outil de questionnaire générique (SF-36) et spécifique (SS-QOL).
- Déterminer le taux de dépression post-AVC (en utilisant le GDS-15) et ses déterminants.
- Calculer les taux de survie à un mois et à un an après un AVC et identifier les prédicteurs de mortalité.

Ces objectifs ont été répartis sur 4 articles scientifiques:

- 1- Facteurs de risque et prise en charge de l'AVC ischémique aigu au Liban: obstacles et solutions.
- 2- Mortalité et prédicteurs de mortalité post-AVC: données d'une cohorte prospective multicentrique de patients Libanais atteints d'AVC.
- 3- Qualité de vie des survivants d'un AVC à un an et de ses prédicteurs: une étude de cohorte prospective multicentrique.

4- Coût médical direct de l'hospitalisation pour AVC aigu au Liban: une étude prospective multicentrique du coût de la maladie basée sur l'incidence.

La réalisation de ces objectifs conduit à l'objectif principal de toute étude épidémiologique: mieux comprendre et prévoir l'évolution d'une maladie et de ses facteurs de risque afin d'améliorer sa prévention primaire et secondaire et limiter son impact physique / psychique / socio-économique sur la population.

ETUDES

Facteurs de risque et prise en charge de l'AVC ischémique aigu au Liban: Obstacles et solutions

Résumé

Introduction et Objectif

La prise en charge de l'AVC aigu varie considérablement d'un pays à l'autre et au sein d'un même pays. Cette étude évalue les pratiques actuelles des médecins au Liban impliqués dans le traitement de l'AVC.

Méthodes

Nous avons mené une étude observationnelle prospective incluant des patients hospitalisés pour AVC aigu du 1er août 2015 au 31 juillet 2016 dans 8 hôpitaux Libanais. Les caractéristiques de base, les études de diagnostic, les traitements pendant l'hospitalisation et à la sortie ont été collectés et analysés.

Résultats

Deux cent trois cas d'AVC ont été enregistrés dont seuls cent soixante-treize patients (85%) présentant un événement ischémique ont été inclus dans l'étude. L'âge moyen était de $69,8 \pm 12,7$ ans. Tous les patients ont fait une imagerie cérébrale (scanner et/ou IRM) à l'admission. Tous les AVC ischémiques ont été gérés par un neurologue et ont eu une consultation avec un cardiologue. L'hypertension était le facteur de risque le plus répandu (78,6%), suivie de l'habitude de fumer (50,3%), du diabète (42,8%), de l'hypercholestérolémie (39,9%), des antécédents d'AVC ou d'AIT (17,3%) et de la fibrillation auriculaire (14,7%). Seuls 4 patients (2,5% des AVC ischémiques) ont reçu un traitement thrombolytique. Plus de 89% des patients ont reçu au moins un médicament antihypertenseur, 89,2% de la statine et 37,6% d'antidiabétique.

Conclusion

Il existe de nombreux défis ainsi que de potentiel d'amélioration des soins de l'AVC au Liban. Les traitements de reperfusion sont encore largement sous-utilisés et restent un défi majeur.

Mots clés: AVC ischémique; management; Liban, facteurs de risque cardiovasculaires

La première étude met en lumière la situation critique des soins de l'AVC aigu dans les hôpitaux Libanais et la nécessité de mettre en place des unités d'AVC organisées pour améliorer la prise en charge aiguë des patients atteints d'AVC. Des campagnes de sensibilisation du public sur les symptômes de l'AVC, les facteurs de risque et la maladie peuvent aider les patients à arriver plus tôt dans les hôpitaux, avant que des lésions cérébrales graves ne se produisent. La situation actuelle dans le pays insiste sur la nécessité de lancer des études épidémiologiques pour évaluer les résultats après un AVC. Les prédictors de la mortalité à court et à long terme peuvent également jouer un rôle majeur dans l'amélioration de la gestion et du pronostic des AVC. Par conséquent, la deuxième étude visait à examiner les taux de mortalité au cours de la première année après un AVC aigu et les principaux prédictors de la mortalité à court terme (1-mois) et à long terme (1-an).

Mortalité et prédicteurs de décès après un AVC: données provenant d'une cohorte prospective multicentrique de patients Libanais atteint d'AVC

Résumé

Introduction et Objectif

Malgré les efforts pour réduire le taux de mortalité par AVC, la maladie reste une des principales causes de décès au Liban, soulignant l'importance de la compréhension des facteurs de risque et de mortalité. Nous avons examiné le taux de mortalité au cours de la première année après AVC ainsi que les prédicteurs de mortalité à court (1-mois) et à long terme (1-an).

Méthodes

Des données ont été collectées de manière prospective sur des patients hospitalisés pour AVC de 8 hôpitaux de Beyrouth au cours d'une période d'un an. Les patients ont été suivis pendant un an ou jusqu'à la mort. Les taux de mortalité ont été évalués à 1-mois et à 1-an après l'AVC et les prédicteurs de décès ont été évalués à l'aide du modèle de risque proportionnel de Cox.

Résultats

Au total, 203 patients victimes d'un AVC ont été inclus. Les données de survie ont été complétées pour plus de 97% des patients. Les taux de mortalité cumulatifs étaient de 13,3% à 1-mois et de 21,2% à 1-an. Les facteurs prédictifs de mortalité à court et à long terme dans l'analyse univariée étaient le faible statut socio-économique, l'admission à l'unité de soins intensifs, le niveau de conscience réduit, la gravité de l'AVC et la présence de complications. L'état civil était également un prédicteur de mortalité à court terme, tandis que l'âge >64 ans et le besoin de chirurgie étaient également des prédicteurs de mortalité à long terme. Dans l'analyse multivariée, la gravité de l'AVC et la présence de complications étaient les prédicteurs de décès à 1-mois et à 1-an. Le faible statut socioéconomique, la dépendance vis-à-vis des activités de la vie quotidienne ainsi que la présence de comorbidités étaient des prédicteurs supplémentaires de mortalité à 1-an.

Conclusion

Environ un patient sur cinq n'a pas survécu un an après un AVC. Une intervention agressive est nécessaire pour améliorer les connaissances, l'alerte et la prévention de l'AVC, afin de réduire ce taux élevé de mortalité par AVC au Liban.

Mots clés: AVC; mortalité; prédicteurs; court terme; long terme; Liban

Les proportions élevées de décès 1-mois et 1-an après un AVC incitent à la nécessité de mettre en œuvre des mesures sérieuses pour améliorer les soins de l'AVC. La dépendance aux activités de la vie quotidienne était l'un des prédictors de mortalité à long terme. La dépendance aux activités de la vie quotidienne entraîne une baisse de la qualité de vie et une dépression. Nous avons donc pensé à évaluer la qualité de vie et le taux de dépression des survivants après 1-an l'AVC ainsi que leurs prédictors.

Qualité de vie des survivants d'un AVC à un an et ses prédicteurs: une étude de cohorte prospective multicentrique

Résumé

Introduction et Objectif

Les AVC ont un impact majeur sur les survivants, notamment sur la qualité de vie liée à la santé (QVLS). Dans ce contexte, il est crucial d'identifier les facteurs influençant la QVLS chez les survivants d'un AVC afin de pouvoir les manipuler efficacement afin de maximiser l'amélioration de la QVLS. Nous avons cherché à évaluer la QVLS des patients un an après l'ACV et leurs prédicteurs.

Méthodes

Cette étude a été conçue comme une étude de cohorte prospective multicentrique dans laquelle 150 patients atteints d'AVC ont été suivis à la sortie de l'hôpital, à 3, 6 et 12 mois après l'AVC. Les niveaux de QVLS ont été déterminés à 1-an en utilisant à la fois l'échelle générique: le Short Form (SF-36) et l'échelle spécifique à la maladie: Stroke Specific Quality Of Life (SS-QOL). Les déterminants de la QVLS ont été recherchés parmi des variables telles que l'âge, le sexe, le statut socio-économique, le type et le nombre d'AVC, l'échelle NIHSS, l'échelle de Rankin modifiée, l'Indice de Barthel et la dépression (en utilisant Geriatric Depression Scale (GDS-15)).

Résultats

Un total de 150 patients victimes d'AVC ont été inclus. La moyenne du SS-QOL était de $3,7 \pm 1,1$ et celle du SF-36 de $57,2 \pm 25,5$. Plus de 15% des patients victimes d'AVC étaient déprimés. Les principaux déterminants de la QVLS étaient le statut fonctionnel, la dépendance aux activités de la vie quotidienne, la gravité de l'AVC, l'âge et la dépression. Le statut fonctionnel et la QVLS (composante physique du SF-36) étaient les principaux déterminants de dépression.

Conclusion

La QVLS des patients victimes d'un AVC est relativement faible. Le fait que le principal déterminant de la QVLS soit le statut fonctionnel suggère qu'il peut être utile d'améliorer l'état fonctionnel physique pour améliorer la QVLS des patients victimes d'un AVC et ainsi réduire le taux élevé de dépression.

Mots-clés: qualité de vie; prédicteurs; AVC; Liban; SF-36; SS-QOL

L'état fonctionnel physique était le principal facteur prédictif de la QVLS. Cependant, le statut émotionnel affecte également la QVLS. Les DALY représentent le fardeau de la maladie pour l'homme. Malgré la prévalence et le fardeau relativement élevés des AVC au Liban, son coût n'est pas connu. La quatrième étude visait donc à quantifier le fardeau de l'AVC en fournissant des données financières détaillées sur le coût direct hospitalier de l'AVC aigu au Liban et à en évaluer ses prédicteurs.

Coût direct médical de l'hospitalisation pour AVC aigu au Liban: étude prospective du coût de la maladie, multicentrique, basée sur l'incidence

Résumé

Introduction et Objectif

Les AVC constituent un problème social et sanitaire majeur qui pèse lourdement sur les économies nationales. Nous avons fourni des données financières détaillées sur le coût direct hospitalier de l'AVC au Liban et en avons évalué les prédicteurs.

Méthodes

Il s'agissait d'une étude observationnelle, quantitative, prospective, multicentrique, basée sur l'incidence du coût de la maladie. Les dossiers médicaux et de facturation des patients ayant subi un AVC admis dans huit hôpitaux de Beyrouth au cours d'une année ont été analysés. Les coûts médicaux directs ont été calculés et les inducteurs de coûts ont été évalués à l'aide d'une analyse de régression linéaire multivariée.

Résultats

Au total, 203 patients ayant subi un AVC ont été inclus (homme: 58%; âge moyen: 68,8±12,9 ans). Le coût direct à l'hôpital pour tous les cas était de 1 413 069 USD pour 2626 jours (538 USD par jour d'hospitalisation). Le coût moyen à l'hôpital par patient ayant subi un AVC était de 6961±15.663 USD. Les AVC hémorragiques étaient les plus coûteux, les accidents ischémiques transitoires étaient les moins coûteux. Les inducteurs de coût étaient la durée du séjour à l'hôpital, la durée du séjour dans l'unité de soins intensifs, le type d'AVC, la gravité de l'AVC, l'échelle de Rankin modifiée, le tiers payeur, la chirurgie et les complications infectieuses.

Conclusion

Le coût médical direct de l'AVC aigu représente un lourd fardeau financier pour le système de santé Libanais. L'élaboration de politiques de santé publique et d'activités de prévention primaire ciblées doit être une priorité pour minimiser l'admission à l'avenir des cas d'AVC et pour limiter ces coûts.

Mots clés: coût de la maladie, coûts hospitaliers, AVC, Liban, études prospectives, politique de la santé, incidence, analyse de régression, humains.

DISCUSSION

Au Liban, nous avons constaté que la gestion des AVC est conforme aux lignes directrices fondées sur des preuves et à la pratique clinique. Cependant, les traitements de reperfusion sont encore largement sous-utilisés et restent un défi majeur. La mortalité par AVC est relativement élevée par rapport à d'autres pays (en particulier la mortalité à court terme). Des campagnes de sensibilisation du public (mettant l'accent sur les personnes à faible niveau d'éducation et statut socio-économique) sur les facteurs de risque de l'AVC, les symptômes et l'importance de traitement temps-dépendant de l'AVC sont nécessaires. La mise en place d'unité de traitement des AVC dans les hôpitaux, ainsi que des protocoles de gestion, constitueront une étape importante dans l'amélioration de la qualité de soins (cliniquement et économiquement). Cela peut limiter le taux de mortalité et les complications possibles après un AVC.

Un contrôle plus agressif des facteurs de risque modifiables et nécessaires pour réduire l'incidence des AVC et donc la mortalité par AVC. L'hypertension artérielle est un facteur important dans la prévention primaire pour plusieurs raisons. L'hypertension artérielle est le facteur de risque le plus puissant des AVC, sa prévalence est élevée au Liban et la prise en charge des patients hypertendus reste sous-optimale. Ainsi, une meilleure prise en charge des patients hypertendus réduira le risque d'AVC.

Améliorer la rééducation physique à l'hôpital et souligner l'importance de la rééducation physique après la sortie de l'hôpital est primordial pour les patients afin d'améliorer leurs fonction physique altérée et de se réintégrer socialement et professionnellement dans la société. Cela diminuera le déclin de la qualité de vie après un AVC qui était relativement élevé dans notre étude et limitera donc le taux de dépression après un AVC. Le fait de pouvoir continuer à travailler après un AVC est fondamental pour l'individu et la société. Cela réduira les coûts indirects (perte de productivité au travail et perte de productivité future) et les DALY.

La gestion globale des AVC à l'hôpital ne différait pas entre le statut socio-économique et le tiers payeur privé par rapport à un tiers payant public, même si le coût hospitalier de l'AVC était très différent. Cela signifie que les patients reçoivent les mêmes soins, quelle que soit leur statut socio-économique et leur tiers payant.

La somme de toutes ces mesures (incidence, prévalence, mortalité, qualité de vie, coût de la maladie, etc.) donnerait une image complète du fardeau de l'AVC au Liban.

Nos conclusions sont importantes pour les professionnels de la santé et les responsables des politiques de santé publique. Lorsque des données fiables sur le fardeau de l'AVC sont disponibles, la planification des soins de santé peut être prise en considération plus efficacement, idéalement avec la génération de données longitudinales pour surveiller utilement l'efficacité de toute intervention. Nos résultats montrent l'importance de réalisation de programmes de prévention primaire et secondaire et des campagnes de sensibilisation sur le danger des facteurs de risque comportementaux pour réduire la morbidité et la mortalité dues aux AVC.

PERSPECTIVES & CONCLUSION

L'AVC est une priorité moins importante pour les services cliniques et de recherche que pour d'autres maladies ayant un impact similaire ou moindre sur la santé publique. Ceci est lié au manque de données comparatives facilement accessibles pour aider à préparer un argument politique en faveur de l'élaboration de stratégies nationales pour faire face au fardeau de l'AVC. Dans le futur proche, il serait intéressant de:

Calculez exactement le taux d'incidence des AVC au Liban.

Analyser les disparités régionales dans l'épidémiologie des AVC et leur influence sur les facteurs de risque et la gestion de la maladie.

Évaluer la connaissance des symptômes et des facteurs de risque de l'AVC et l'attitude de la population envers les AVC.

Estimer le rapport coût-efficacité des unités intégrées spécialisées pour AVC au Liban: améliorer les résultats pour les patients par rapport aux soins classiques.

Évaluer la prise en charge chronique des AVC: prévention secondaire (évaluation de l'observance aux traitements des patients victimes d'un AVC, suivi médical, examens de routine, contrôle des facteurs de risque, taux de récurrence d'AVC, etc.), soins de réadaptation chronique, taux de mortalité tardive et prévalence d'handicap due à l'AVC.

Rechercher de solutions thérapeutiques plus efficaces pour prévenir les séquelles d'AVC est indispensable. Cela comprend l'utilisation de cellules souches et la recherche de nouveaux agents neuroprotecteurs.

Plus de recherche dans les domaines de l'hypothermie (refroidissement thérapeutique), des thérapies à base de cellules souches et d'une "polypill" pour la prévention secondaire des AVC est nécessaire.

Un autre sujet intéressant est de déterminer la qualité de vie des fournisseurs de soins aux patients victimes d'un AVC et de ses déterminants. De plus, il peut être raisonnable de déterminer le taux de dépression chez les fournisseurs de soins aux patients victimes d'un AVC et ses déterminants.

Les études présentées dans ce manuscrit peuvent éventuellement être répétées, mais d'une manière qui permet de les généraliser à l'ensemble du pays (meilleur échantillonnage de tous les gouvernorats, échantillon de plus grande taille, etc.) dans la communauté et pas uniquement dans les hôpitaux, en mesurant les facteurs de risque socio-économiques (éducation, travail, revenu), facteurs psychiques (stress et anxiété), toutes les comorbidités et les facteurs de risque potentiels.

Il est absolument nécessaire de développer nos connaissances sur l'épidémiologie des AVC au Liban, afin de limiter l'impact et le fardeau de la maladie dans les années à venir.

LIST OF SCIENTIFIC PRODUCTIONS

Published articles:

Abdo R, Abboud H, Salameh P, Jomaa N, Rizk R, Hosseini H. Direct Medical Cost of Hospitalization for Acute Stroke in Lebanon: A Prospective Incidence-Based Multicenter Cost-of-Illness Study. Inquiry. 2018 Jan-Dec;55:46958018792975. doi: 10.1177/0046958018792975. PubMed PMID: 30111269.

Submitted articles:

Mortality and predictors of death post stroke: Data from a multicenter prospective cohort of Lebanese stroke patients. **Abdo R**, Abboud H, Salameh P, El Hajj T, Hosseini H. Under revision in Journal of Stroke & Cerebrovascular Diseases.

Risk factors and acute ischemic stroke management in Lebanon: Obstacles and Solutions. **Abdo R**, Hosseini H, Salameh P, Rizk R, Abboud H. Under revision in Cerebrovascular Diseases Journal

Quality of life of 1-year stroke survivors and its predictors: a multicenter prospective cohort study. **Abdo R**, Abboud H, Salameh P, Rizk R, Hosseini H. Under revision in

Oral communication:

Speaker at the Eighth International Congress of the Lebanese Society of Neurology (LSN). Beirut 2016. **Abdo R**. Cost of Acute Stroke in Lebanon.

Speaker at the 26th Annual Congress of the Lebanese Order of Pharmacists (OPL). Beirut 2018. **Abdo R**. Acute stroke management and short-term and long-term outcomes post-stroke in Lebanon.

Poster with discussion:

21^{ème} édition des Journées de Neurologie de Langue Française (JNLF). Toulouse 2017. **Abdo R**, Abboud H, Salameh P, Hosseini H. Coût direct hospitalier des accidents vasculaires cérébraux au Liban

The 3rd European Stroke Organisation Conference (ESOC) Prague 2017. **Abdo R**, Abboud H, Salameh P, Hosseini H. Sex disparities in stroke care and recovery in Lebanon.

The 26th European Stroke Conference (ESC) Berlin 2017. **Abdo R**, Abboud H, Salameh P, Hosseini H. Acute ischemic stroke management in Lebanon.

The 3rd European Academy of Neurology (EAN). Amsterdam 2017. **Abdo R**, Abboud H, Salameh P, Hosseini H. Cost of acute stroke in Lebanon.

The 4th European Stroke Organisation Conference (ESOC). Gothengurb 2018. **Abdo R**, Abboud H, Salameh P, Hosseini H. Predictors of in-hospital and 1-year mortality after stroke

The 4th European Academy of Neurology (EAN). Lisbon 2018. **Abdo R**, Abboud H, Salameh P, Hosseini H. Long-term outcome of stroke patients: Data from a multicenter cohort of Lebanese stroke patients.

LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
AHA	American Heart Association
AHI	Apnea-Hypopnea Index
AIS	Acute Ischemic Stroke
ARIC	Atherosclerosis Risk In Communities
BP	Blood Pressure
CHD	Coronary Heart Disease
CI	Confidence Interval
CT	Computed Tomography
CVD	Cardiovascular disease
DALY	Disability-Adjusted Life Year
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
GFR	Glomerular Filtration Rate
HBP	High Blood Pressure
HD	Heart Disease
HDL-C	High Density Lipoproteins Cholesterol
HIC	High Income Countries
HR	Hasard Ratio
ICH	Intracerebral Hemorrhage
INR	Intermational Normalized Ratio
IS	Ischemic stroke
LDL-C	Low Density Lipoproteins Cholesterol
LIMC	Low- and Middle-Income Countries
LOE	Level Of Evidence
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NCCT	Noncontrast CT
NHLBI	National Heart, Lung and Blood Institute
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
OR	Odds Ratio
PA	Physical Activity
QOL	Quality Of Life
RCT	Randomized Control Trial
RR	Relative Risk
rtPA	recombinant tissue Plasminogen Activator
SAH	Subarachnoid hemorrhage
SBP	Systolic Blood Pressure
TC	Total Cholesterol
TIA	Transient Ischemic Attack
US	United States
WHO	World Health Organization

TABLE OF CONTENT

Contents

1. INTRODUCTION	42
1.1. STROKE	43
1.1.1. DEFINITION	43
1.1.2. TYPE OF STROKE	43
1.2 Transient ischemic attack.....	50
1.2.1. Definition.....	50
1.2.2. Prevalence, Incidence, and Prognosis	51
1.3 Recurrent Stroke	52
1.4. Risk factors	54
1.4.1. Controllable risk factors	54
1.4.2. Uncontrollable risk factors	69
1.4.3. Additional factors	75
1.5 Recognizing signs of stroke	77
1.6 EARLY MANAGEMENT OF SROKE	78
1.6.1. Emergency Evaluation and Diagnosis of AIS	78
1.6.2. Early Diagnosis: Brain and Vascular Imaging.....	80
1.6.3. General Supportive Care and Treatment of Acute Complications.....	83
1.6.4. Intravenous Fibrinolysis	85
1.6.5. Endovascular Interventions.....	87
1.6.6. Anticoagulants.....	89
1.6.7. Antiplatelet Agents.....	89
1.6.8. Volume Expansion, Vasodilators, and Induced Hypertension	90
1.6.9. Neuroprotective agents	91
1.6.10. Surgical Interventions.....	91
1.6.11. Admission to the Hospital and General Acute Treatment (After Hospitalization).....	92
1.6.12. Treatment of Acute Neurological Complications	93
1.7 Management of Spontaneous Intracerebral Hemorrhage	94
1.7.1. Prehospital Management.....	94
1.7.2. Emergency Diagnosis and Assessment.....	94
1.7.3. Medical Treatment for ICH.....	94
1.7.4. General Monitoring and Nursing Care	95
1.7.5. Seizures and Antiseizure Drugs	95
1.7.6. Management of Medical Complications	96

1.7.7.	Procedures/Surgery.....	96
1.7.8.	Prevention of Recurrent ICH	97
1.7.9.	Rehabilitation and Recovery	98
1.8.	Global Burden of Stroke	98
1.8.1.	Stroke Prevalence.....	98
1.8.2.	Stroke Incidence.....	99
1.8.3.	Stroke Mortality	100
1.8.4.	Disability-adjusted life years	107
1.8.5.	Quality Of Life post-stroke	109
1.8.6.	Stroke clinical outcome and measures	113
1.8.7.	Cost of Stroke	116
2.	Situation in Lebanon	121
3.	Objectives.....	124
4.	Studies.....	126
5.	Discussion.....	212
5.1	Discussion of the main results of the thesis.....	213
5.2	Implications of outcomes for public health policy makers	214
6.	Perspectives & Conclusion	215
7.	REFERENCES	218

Appendix

Appendix 1:	Stroke definitions.....	241
Appendix 2:	NIH Stroke Scale	242
Appendix 3:	SF-36 questionnaires	248
Appendix 4:	Stroke Specific Quality of Life Scale (SS-QOL) questionnaire.....	253
Appendix 5:	Geriatric Depression Scale (Short Form) questionnaire.....	255
Appendix 6:	In-hospital questionnaire	256
Appendix 7:	Submitted article.....	271

LIST OF FIGURES

FIGURE 1 ISCHEMIC STROKE ILLUSTRATION.....	44
FIGURE 2 BAMFORD OR OXFORD STROKE CLASSIFICATION	48
FIGURE 3 SUBARACHNOID HEMORRHAGE STROKE ILLUSTRATION (AMERICAN HEART ASSOCIATION 2018)	50
FIGURE 4 INTRACEREBRAL HEMORRHAGE STROKE ILLUSTRATION (AMERICAN HEART ASSOCIATION 2018).....	50
FIGURE 5 RISK OF STROKE FOLLOWING A TIA	52
FIGURE 6 ILLUSTRATION OF CARDIOVASCULAR TISSUES AGING	70
FIGURE 7 PREVALENCE OF STROKE BY AGE AND SEX (NHANES 2011–2014).....	71
FIGURE 8 ANNUAL AGE-ADJUSTED INCIDENCE OF FIRST-EVER STROKE BY RACE.....	73
FIGURE 9 "ACT F.A.S.T." CAMPAIGN TO RAISE AWARENESS OF STROKE SYMPTOMS AND TIME IMPORTANCE..	77
FIGURE 10 "BE FAST" CAMPAIGN TO RAISE AWARENESS OF STROKE SYMPTOMS AND TIME IMPORTANCE	78
FIGURE 11 STROKE INCIDENCE AGE-ADJUSTED TO THE WHO WORLD POPULATION.....	99
FIGURE 12 STROKE INCIDENCE IN THE WORLD (PER 100,000 PERSON-YEARS) (FEIGIN ET AL., 2014)	100
FIGURE 13 TOP 10 GLOBAL CAUSES OF DEATHS, 2016 (WHO 2018)	101
FIGURE 14 TOP 10 CAUSES OF DEATHS IN HIGH-INCOME COUNTRIES, 2016 (WHO 2018).....	102
FIGURE 15 TOP 10 CAUSES OF DEATHS IN UPPER-MIDDLE-INCOME COUNTRIES, 2016 (WHO 2018)	102
FIGURE 16 TOP 10 CAUSES OF DEATHS IN LOWER-MIDDLE-INCOME COUNTRIES, 2016 (WHO 2018)	103
FIGURE 17 TOP 10 CAUSES OF DEATHS IN LOW-INCOME COUNTRIES, 2016 (WHO 2018)	103
FIGURE 18 STROKE DEATH RATES, TOTAL POPULATION 35+, 2014 THROUGH 2016	104
FIGURE 19 TRENDS IN CONTRIBUTION TO DEATH DUE TO ISCHEMIC AND HEMORRHAGIC STROKE AS A PERCENTAGE OF ALL CONDITIONS BETWEEN DEVELOPED AND DEVELOPING COUNTRIES	106
FIGURE 20 PROBABILITY OF DEATH WITHIN 1-YEAR AFTER FIRST STROKE.....	107
FIGURE 21 PROJECTED TRENDS FOR STROKE DEATHS BY WORLD BANK INCOME GROUP 2002-30.....	107
FIGURE 22 TRENDS IN CONTRIBUTION TO DALYs DUE TO ISCHEMIC AND HEMORRHAGIC STROKE AS A PERCENTAGE OF ALL CONDITIONS BETWEEN DEVELOPED AND DEVELOPING COUNTRIES	108
FIGURE 23 THE MODIFIED RANKIN SCALE	114
FIGURE 24 THE BARTHEL ADL INDEX GUIDELINES.....	114
FIGURE 25 THE BARTHEL ADL INDEX.....	115
FIGURE 26 COSTS ATTRIBUTABLE TO STROKE IN EUROPE IN 2010.	119

LIST OF TABLES

TABLE 1 TOAST CLASSIFICATION OF SUBTYPES OF ACUTE ISCHEMIC STROKE.....	46
TABLE 2 FEATURES OF TOAST CLASSIFICATION OF SUBTYPES OF ISCHEMIC STROKE.....	47
TABLE 3 CHADS2 SCORE: STROKE RISK ASSESSMENT IN ATRIAL FIBRILLATION	64
TABLE 4 CHADS2 SCORE AND CORRESPONDING ANNUAL STROKE RISK	65
TABLE 5 CHA2DS2-VASC SCORE AND RISK CRITERIA	65
TABLE 6 CHA2DS2-VASC SCORE AND CORRESPONDING ANNUAL STROKE RISK.....	65
TABLE 7 TREATMENT RECOMMENDATIONS BASED ON CHA2DS2-VASC SCORE (JANUARY ET AL., 2014)	66
TABLE 8 HAS-BLED BLEEDING RISK SCORE	66
TABLE 9 HAS-BLED SCORE INTERPRETATION.....	66
TABLE 10 OPTIONS TO TREAT ARTERIAL HYPERTENSION IN PATIENTS WITH AIS WHO ARE CANDIDATES FOR ACUTE REPERFUSION THERAPY*	83

1. INTRODUCTION

1.1. STROKE

1.1.1. DEFINITION

The World Health Organization (WHO) definition of stroke is: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death (or if the development of symptoms is interrupted by a surgical intervention), with no apparent cause other than of vascular origin”. It includes patients presenting clinical signs and symptoms suggestive of subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH) or cerebral ischemic necrosis (**Appendix 1**). Global clinical signs are accepted only in cases of subarachnoid hemorrhage or in patients with deep coma. Brain lesions detected by CT scan but not accompanied by acute focal signs are not accepted as stroke, nor are extradural and subdural hemorrhages. This definition does not include transient ischemic attack (TIA) or stroke events in cases of blood disease (e.g. leukemia, polycythaemia vera), brain tumor or brain metastases. Patients with stroke symptoms caused by poisoning and secondary stroke caused by trauma should also be excluded (Truelsen et al., 2000; WHO MONICA Project Investigators, 1988).

1.1.2. TYPE OF STROKE

The pathological background for stroke may either be ischemic or hemorrhagic disturbances of the cerebral blood circulation.

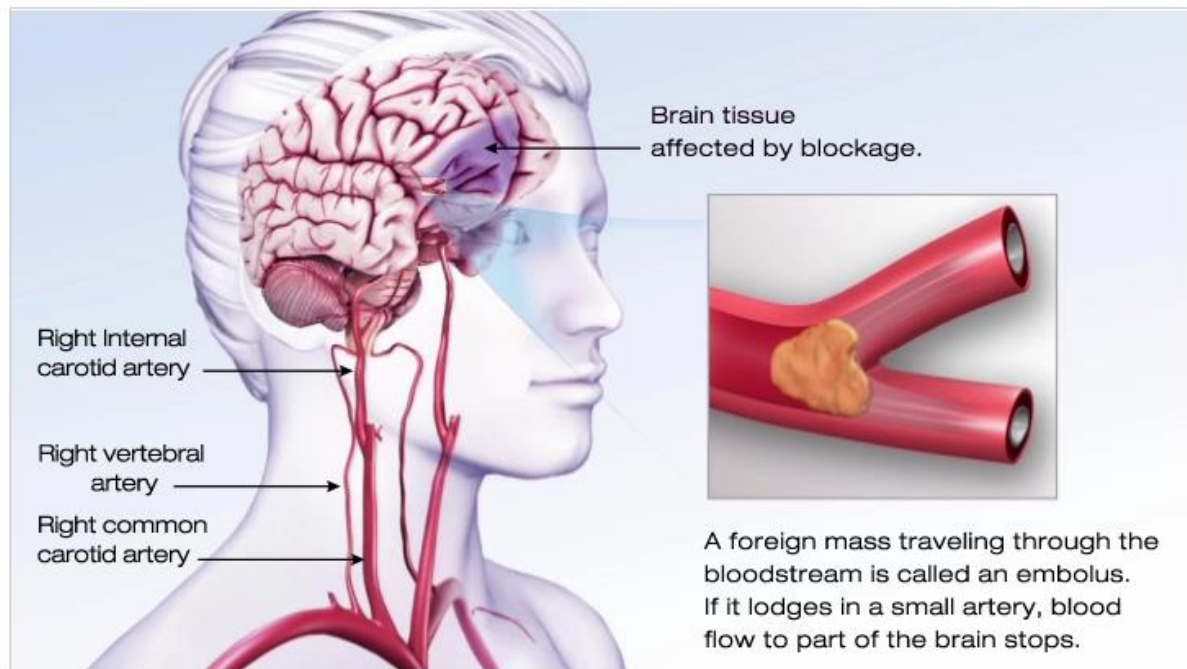
1.1.2.1 Ischemic stroke (infarction)

Ischemic stroke (IS) accounts for about 87% of all cases. ISs occur as a result of an obstruction of large cervical and cerebral arteries, with ischemia in all or part of the territory of the occluded artery. The underlying condition for this type of obstruction is the development of fatty deposits lining the vessel walls, known as atherosclerosis. These fatty deposits can cause two types of obstruction:

- **Cerebral thrombosis** refers to a thrombus (blood clot) that develops at the clogged part of the vessel (occlusion at the site of the main atherosclerotic lesion).
- **Cerebral embolism** refers generally to a blood clot that forms at another location in the circulatory system, usually the heart (cardiac lesions, either at the site of the valves or of the heart cardiac cavities) and large arteries of the upper chest and neck. A portion of the blood clot breaks loose, enters the bloodstream and travels through the brain's blood vessels until it reaches vessels too small to let it pass. A second important cause of

embolism is an irregular heartbeat or rhythm disturbances with stasis of the blood, known as atrial fibrillation (AF). It creates conditions where clots can form in the heart, dislodge and travel to the brain (**Figure 1**).

Silent cerebral infarction, or “silent stroke,” is a brain injury likely caused by a blood clot interrupting blood flow in the brain. It’s a risk factor for future strokes which could lead to progressive brain damage due to these strokes (AHA/ASA; 2018).



Source: American Heart Association 2018

Figure 1 Ischemic stroke illustration

TOAST Subtype Classification System

Diagnoses are based on clinical features and on data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state. The physician can apply the clinical and imaging findings when first assessing the patient and then consider the results of other diagnostic tests later. An important part of the classification is the ability of the physician to categorize a specific subtype diagnosis as probable or possible based on the degree of certainty. A "probable" diagnosis is made if the clinical findings, neuroimaging data, and results of diagnostic studies are consistent with one subtype and other etiologies have been excluded. A "possible" diagnosis is made when the clinical findings and neuroimaging data suggest a specific subtype but other studies are not done. Because many patients will have a limited number of diagnostic tests, the probable and

possible subcategorizations allow the physician to make as precise a subgroup diagnosis as can be achieved (Adams et al., 1999).

The TOAST classification denotes 5 subtypes of IS (**Table 1**):

1) large-artery atherosclerosis: 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, presumably due to atherosclerosis (**Table 2**). Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. A history of intermittent claudication, TIAs in the same vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI 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. Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary to large-artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only minimal changes (Adams et al., 1999).

2) cardioembolism: This category includes patients with arterial occlusions presumably due to an embolus arising in the heart (**Table 2**). Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism (Goldstein et al., 1989) (**Table 3**). At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic sources of thrombosis or embolism should be eliminated. A stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke (Adams et al., 1999).

3) small-vessel occlusion (lacune): This category includes patients whose strokes are often labeled as lacunar infarcts in other classifications (Bamford et al., 1987) (**Table 2**). Lacunar cerebral infarctions are small deep infarcts in the territory of small penetrating arteries, due to a local disease of these vessels, mainly related to chronic hypertension. The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of

cerebral cortical dysfunction. A history of diabetes mellitus (DM) or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated. Potential cardiac sources for embolism should be absent, and evaluation of the large extracranial arteries should not demonstrate a stenosis of greater than 50% in an ipsilateral artery. Lacunes account for 15-25% of all IS (Bamford et al., 1987; Bejot et al., 2008; Sacco et al., 2006). The incidence of lacunar strokes increases with age (mean age of first lacunar stroke, 65 y), and men may be affected more than women (Bejot et al., 2008) (Adams et al., 1999).

4) stroke of other determined etiology: This category includes patients with rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. Patients in this group should have clinical and CT or MRI findings of an acute ischemic stroke (AIS), regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded by other studies (Adams et al., 1999).

5) stroke of undetermined etiology: In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients will have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the evaluation was cursory. This category also includes patients with two or more potential causes of stroke so that the physician is unable to make a final diagnosis. For example, a patient with a medium-risk cardiac source of embolism who also has another possible cause of stroke identified would be classified as having a stroke of undetermined etiology. Other examples would be a patient who has AF and an ipsilateral stenosis of 50%, or the patient with a traditional lacunar syndrome and an ipsilateral carotid stenosis of 50% (Adams et al., 1999).

Table 1 TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified

- b. Negative evaluation
- c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Possible or probable depending on results of ancillary studies.

Table 2 Features of TOAST Classification of Subtypes of Ischemic Stroke

Features	Subtype			
	Large-artery atherosclerosis	Cardioembolism	Small-artery occlusion (lacune)	Other cause
Clinical				
Cortical or cerebellar dysfunction	+	+	-	+/-
Lacunar syndrome	-	-	+	+/-
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct >1.5 cm	+	+	-	+/-
Subcortical or brain stem infarct <1.5 cm	-	-	+/-	+/-
Tests				
Stenosis of extracranial internal carotid artery	+	-	-	-
Cardiac source of emboli	-	+	-	-
Other abnormality on tests	-	-	-	+
TOAST, Trial of Org 10172 in Acute Stroke Treatment.				

Table 3 TOAST Classification of High- and Medium-Risk Sources of Cardioembolism

High-risk sources

- Mechanical prosthetic valve
- Mitral stenosis with atrial fibrillation
- Atrial fibrillation (other than lone atrial fibrillation)
- Left atrial/atrial appendage thrombus
- Sick sinus syndrome
- Recent myocardial infarction (4 weeks)
- Left ventricular thrombus
- Dilated cardiomyopathy
- Akinetic left ventricular segment
- Atrial myxoma
- Infective endocarditis

Medium-risk sources

- Mitral valve prolapse
 - Mitral annulus calcification
 - Mitral stenosis without atrial fibrillation
 - Left atrial turbulence (smoke)
 - Atrial septal aneurysm
 - Patent foramen ovale
 - Atrial flutter
 - Lone atrial fibrillation
 - Bioprosthetic cardiac valve
 - Nonbacterial thrombotic endocarditis
 - Congestive heart failure
 - Hypokinetic left ventricular segment
 - Myocardial infarction (>4 weeks, <6 months)
-

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Bamford or Oxford stroke classification

Bamford (or Oxford) classification system is the most commonly used classification system for IS (Figure 2).

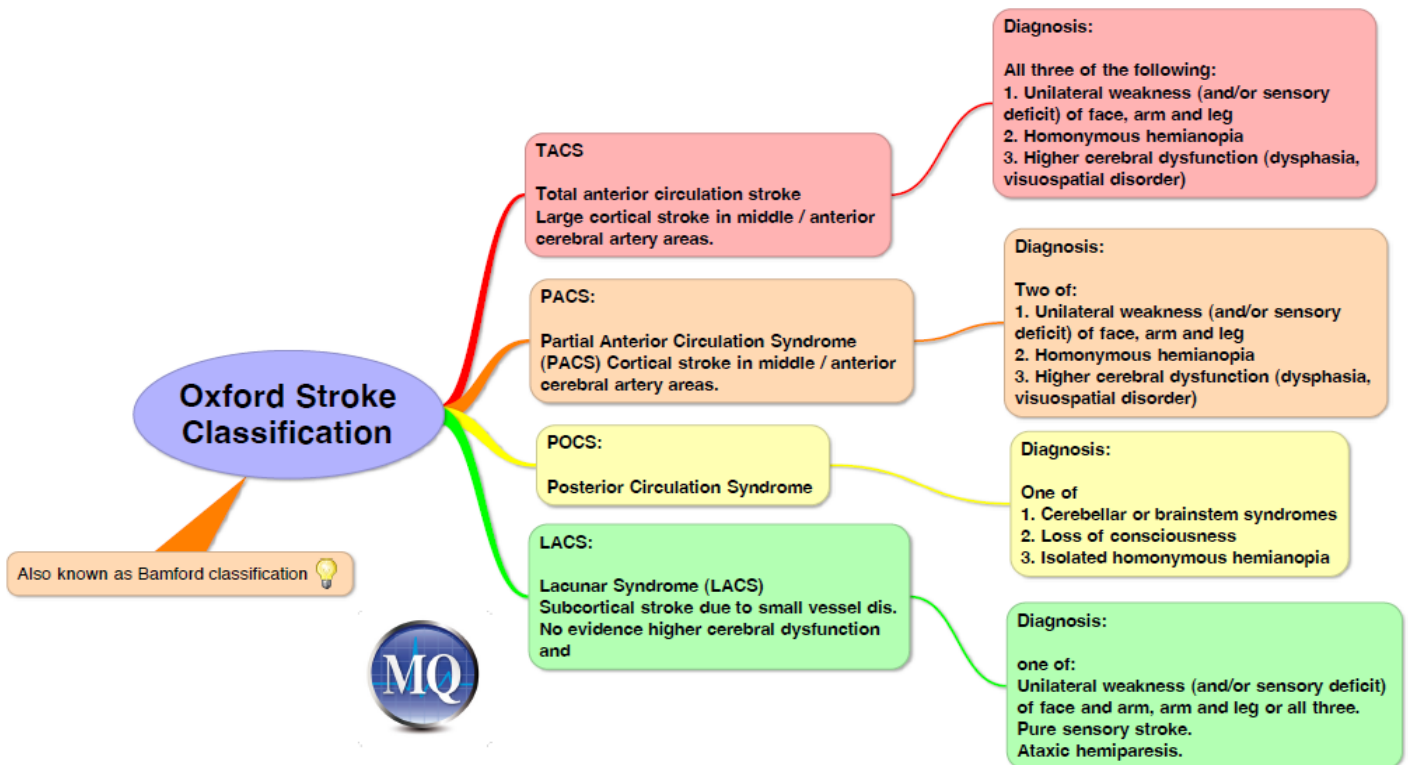


Figure 2 Bamford or Oxford Stroke Classification

1.1.2.2 Hemorrhagic stroke

Hemorrhagic stroke accounts for about 13% of stroke cases.

It results from a weakened vessel that ruptures and bleeds into the surrounding brain. The blood accumulates and compresses the surrounding brain tissue. The two types of hemorrhagic strokes are ICH (within the brain) (10%) or SAH (3%). (Kleindorfer et al., 2005; NINDS, 1999).

Hemorrhagic stroke occurs when a weakened blood vessel ruptures. Two types of weakened blood vessels usually cause hemorrhagic stroke: aneurysms and arteriovenous malformations.

- An **aneurysm** is a ballooning of a weakened region of a blood vessel. If left untreated, the aneurysm continues to weaken until it ruptures and bleeds into the brain.

If an aneurysm ruptures, it leaks blood into the space around the brain. This is called a “SAH” (**Figure 3**). This group of strokes is mainly due to the rupture of aneurysms at the bifurcations of large arteries at the inferior surface of the brain. Often they do not cause direct damage to the brain and some studies of stroke have therefore excluded them. However, patients with SAH may develop symptoms that are in accordance with the stroke definitions and should as such be regarded as a stroke (Truelsen et al.; 2000).

The hemorrhage may also damage the brain directly, usually from bleeding into the brain itself. This is called a “hemorrhagic stroke” (AHA/ASA, 2018) (**Figure 4**).

- An **arteriovenous malformation** is a cluster of abnormally formed blood vessels. Any one of these vessels can rupture, also causing bleeding into the brain (AHA/ASA, 2018).

Spontaneous ICHs (as opposed to traumatic ones) are mainly due to arteriolar hypertensive disease, and more rarely due to coagulation disorders, vascular malformation within the brain, and diet (such as high alcohol consumption, low blood cholesterol concentration, high blood pressure (HBP), etc.). Cortical amyloid angiopathy (a consequence of hypertension) is a cause of cortical hemorrhages especially occurring in elderly people and it is becoming increasingly frequent as populations become older (Truelsen et al.; 2000).

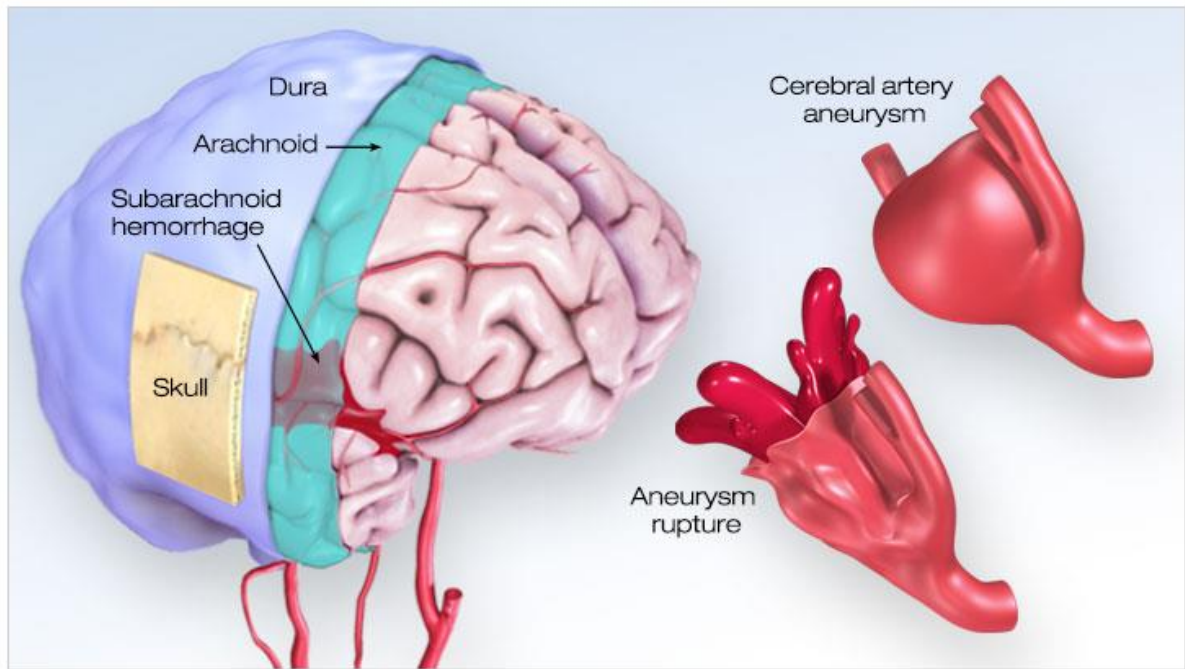


Figure 3 Subarachnoid hemorrhage stroke illustration (American Heart Association 2018)

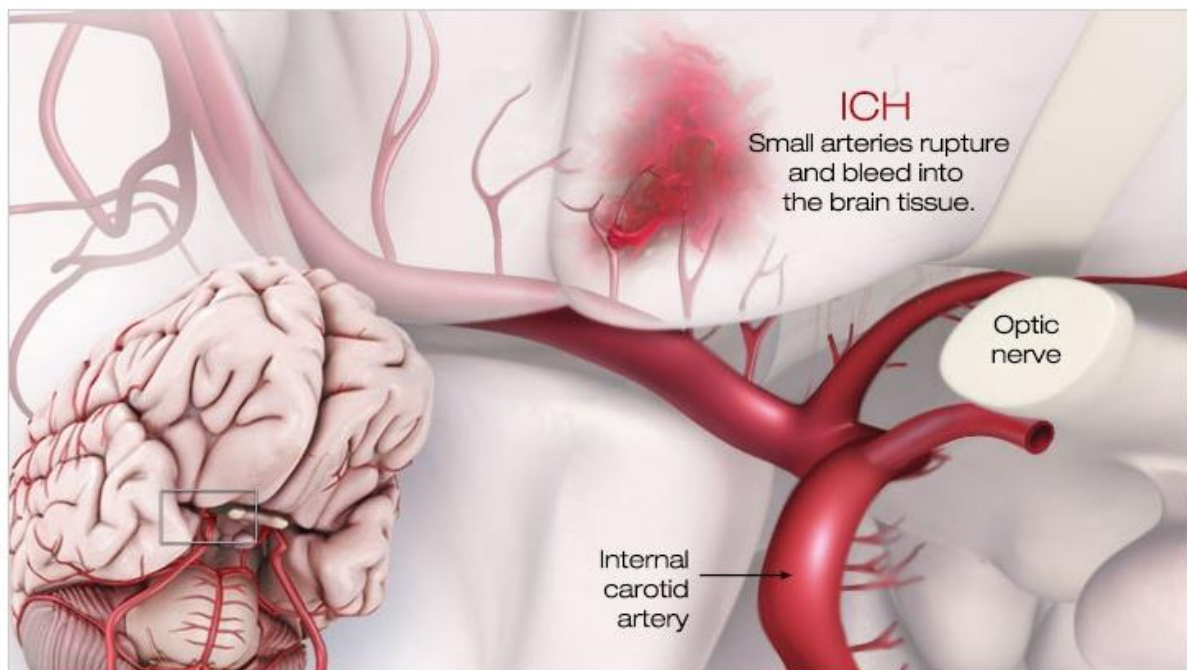


Figure 4 Intracerebral hemorrhage stroke illustration (American Heart Association 2018)

1.2 Transient ischemic attack

1.2.1. Definition

TIA is a "mini stroke" or 'warning stroke' that occurs when a blood clot blocks an artery for a short time. The only difference between a stroke and TIA is that with TIA the blockage is transient (temporary) (AHA/ASA, 2017). TIA is defined as a brief episode of neurologic

dysfunction resulting from focal temporary cerebral ischemia and not associated with cerebral infarction (Easton et al., 2009). TIA symptoms occur rapidly and last a relatively short time. Unlike a stroke, when a TIA is over, there's no permanent injury to the brain. There's no way to tell if symptoms of a stroke will lead to a TIA or a major stroke (AHA/ASA).

1.2.2. Prevalence, Incidence, and Prognosis

1.2.2.1 Prevalence

In a nationwide survey of United States (US) adults, the estimated prevalence of self-reported physician-diagnosed TIA increased with age and was 2.3% overall, which translates to \approx 5 million people. The true prevalence of TIA is likely to be greater, because many patients who experience neurological symptoms consistent with a TIA fail to report it to their healthcare provider (Johnston et al., 2003).

1.2.2.2 Incidence

In the GCNKSS, according to data from 1993 and 1994, the age-, sex-, and race-adjusted incidence rate for TIA was 0.83 per 10 000 (Kleindorfer et al., 2005). In a more recent Italian community-based registry conducted in 2007 to 2009, the crude TIA incidence rate was 0.52 per 1000 (Cancelli et al., 2011).

Incidence of TIA increases with age and varies by sex and race/ethnicity. Men, blacks, and Mexican Americans have higher rates of TIA than their female and non-Hispanic white counterparts (Kleindorfer et al., 2005; Morgenstern et al., 2004).

1.2.2.3 Prognosis

Approximately 15% of all strokes are heralded by a TIA (Hankey, 1996). TIAs confer a substantial short-term risk of stroke, hospitalization for cardiovascular disease (CVD) events, and death. Of 1707 TIA patients, 180 (11%) experienced a stroke within 90 days, and 91 (5%) had a stroke within 2 days. Predictors of stroke included age $>$ 60 years, DM, focal symptoms of weakness or speech impairment, and symptoms that lasted $>$ 10 minutes (Johnston et al., 2000). Meta-analyses of cohorts of patients with TIA have shown the short-term risk of stroke after TIA to be \approx 3% to 10% at 2 days and 9% to 17% at 90 days (Giles et al., 2007; Wu et al., 2007) (**Figure 5**). One in 12 people could have a stroke within a week of having a TIA (Johnston et al., 2000).

Risk of stroke following a TIA

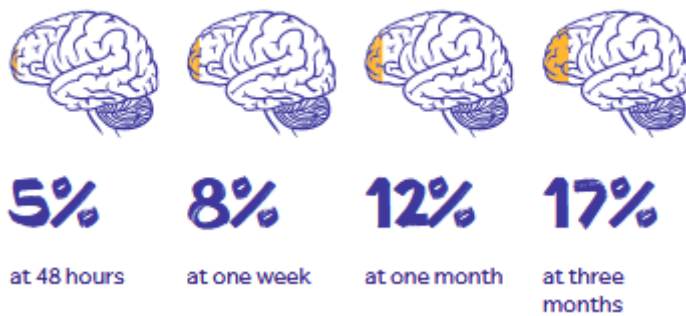


Figure 5 Risk of stroke following a TIA

Individuals who have a TIA and survive the initial high-risk period have a 10-year stroke risk of roughly 19% and a combined 10-year stroke, myocardial infarction (MI), or vascular death risk of 43% (4% per year) (Clark et al., 2003). In the GCNKSS, the 1-year mortality rate after a TIA was 12% (Kleindorfer et al., 2005).

In the population-based Oxford Vascular Study, among patients with TIA, disability levels (modified Rankin Scale >2) increased from 14% before the TIA to 23% at 5 years after the TIA ($P=0.002$). In this same study, the 5-year risk of institutionalization after TIA was 11% (Luengo-Fernandez et al., 2013).

1.3 Recurrent Stroke

In a cohort of 10 399 patients discharged with a primary diagnosis of stroke in the US in 2002, recurrent stroke rates were 1.8% at 1 month, 5% at 6 months, 8% at 1 year, and 18.1% at 4 years (Feng et al., 2010).

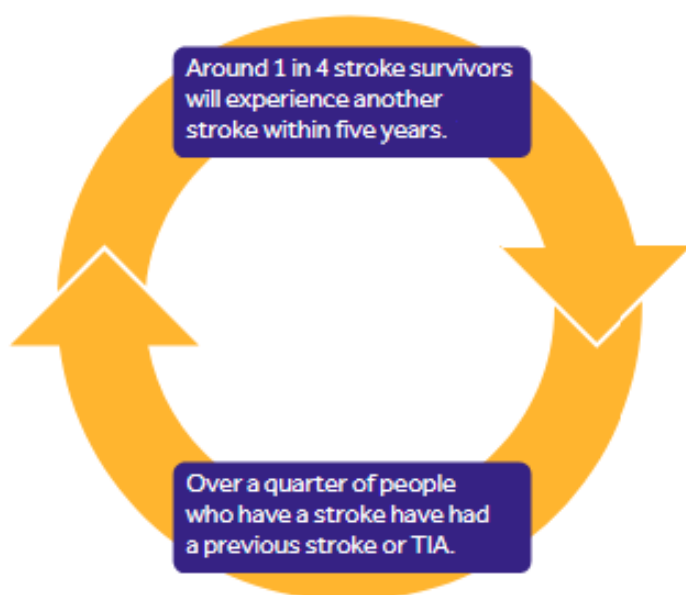
Among 1626 first-ever stroke patients in the South London Stroke Register, first stroke recurrence rates (95% CI) during the first, second, third, fourth, and fifth years were 8% (6.5%–9.8%), 3.3% (2.2%–4.9%), 3.5% (2.1%–5.8%), 1.2% (0.4%–3.7%), and 1.8% (0.4%–7.4%), respectively. Cumulative risks of first stroke recurrence (95% CI) were 2.6% (1.9%–3.7%) at 3 months, 8.0% (6.5%–9.8%) at 1 year, 14.1% (11.8%–16.7%) at 3 years, and 16.6% (13.5%–20.4%) at 5 years (Hillen et al., 2003).

Among 600 Scandinavian stroke patients followed up for 2 years, 55 (9.2%) had a recurrent stroke, 15 (2.5%) had a TIA, 4 (0.7%) had a coronary event, and 24 (4.0%) had died. Recurrent stroke occurred in 19.2% of patients with index stroke caused by large-artery disease, 4.9% with small-vessel disease, 8.2% with cardioembolic cause, 5.6% with cryptogenic cause, and

12.8% with other and undetermined causes combined (Redfors et al., 2012). Recurrent stroke is associated with a greater number of risk factors and a higher incidence of large-artery atherosclerosis than the first stroke (Lee et al., 2001). During a median 5.3 years of follow-up among 987 Atherosclerosis Risk in Communities (ARIC) participants with first-ever strokes, there were 183 recurrent strokes among 147 participants. Approximately 70% of recurrent strokes were of the same subtype; however, 28% were the same when the index stroke was lacunar. One-year stroke recurrence rates by index subtype were 7.9% for thrombotic, 6.5% for cardioembolic, and 6.5% for lacunar events (Jones et al., 2013).

In a long-term follow-up study of recurrent vascular events among 724 first-ever TIA, stroke, or ICH patients aged 18 to 50 years in the Netherlands, cumulative 20-year risk of recurrent stroke was 17.3% (95% CI, 9.5%–25.1%) after TIA, 19.4% (95% CI, 14.6%–24.3%) after IS, and 9.8% (95% CI, 1.0%–18.7%) after ICH (Rutten-Jacobs et al., 2013). Among 1867 stroke patients aged 18 to 45 years, the 10-year cumulative risk of brain ischemia was 14.0% (95% CI, 11.4%–17.1%) (Pezzini et al., 2014). In the North Dublin Population Stroke Study, the cumulative 2-year stroke recurrence rate was 10.8%, and case fatality was 38.6% (Callaly et al., 2016).

Stroke survivors are at greatest risk of having another stroke in the first 30 days following a stroke (Mohan et al., 2011). In fact, 1 in 20 stroke patients have another stroke while still in hospital (Royal College of Physicians SSNAP, 2016).



(Johnston et al., 2000)

1.4. Risk factors

1.4.1. Controllable risk factors

Around 80% of strokes can be prevented (D'Agostino et al., 1994).

1.4.1.1 Hypertension

High blood pressure (HBP) or hypertension, defined as values ≥ 140 mmHg SBP and/or ≥ 90 mmHg DBP (Mancia et al., 2013) (**Table 4**), is the leading cause of stroke and the most significant controllable risk factor for stroke (both IS and intracranial hemorrhage) (Goff et al., 2014).

Table 4 Classification of office blood pressure levels (mmHg)^a

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	<90

^a The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

According to the INTERSTROKE study, the risk of stroke attributable to hypertension reaches 35% for all stroke (O'Donnell et al., 2010). About three in every four people (77%) who have a first stroke have blood pressure (BP) higher than 140/90 mm Hg (Neal et al., 2000).

The risk for stroke and heart disease (HD) mortality increases in a log-linear fashion from SBP levels <115 mm Hg to >180 mm Hg and from DBP levels <75 mm Hg to >105 mm Hg. Each 20 mm Hg higher SBP and 10 mm Hg higher DBP is associated with a doubling in the risk of death caused by stroke, HD, or other vascular disease (Lewington et al., 2003).

In a meta-analysis of clinical trials, antihypertensive therapy was associated with decline in stroke incidence (Law et al., 2009). In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence, with an average 41% reduction in stroke risk with SBP reductions of 10 mm Hg (Pezzini et al., 2014). Diabetic subjects with BP <120/80

mm Hg have approximately half the lifetime risk of stroke of subjects with hypertension. The treatment and lowering of BP among diabetic hypertensive individuals was associated with a significant reduction in stroke risk (Cushman et al., 2010).

A review identified the benefit of intense BP reduction and reduced stroke outcome risks in recent clinical trials (Lackland et al., 2016). Combined results from 2 trials demonstrated that intensive BP control (<120 mm Hg) compared with standard treatment (<140 mm Hg) resulted in a significantly lower risk of stroke (RR, 0.75; 95% CI, 0.58–0.97) (Perkovic et al., 2015).

Several studies have shown significantly lower rates of recurrent stroke with lower BPs. Most recently, the BP reduction component showed that targeting an SBP <130 mm Hg was likely to reduce recurrent stroke by ≈20% ($P=0.08$) and significantly reduced ICH by two-thirds compared with an SBP goal of 130 to 149 mm Hg (SPS3 study group, 2013).

1.4.1.2 **Smoking**

Recent studies confirm that cigarette smoking is another crucial risk factor for stroke. Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for >10 years (Meschia et al., 2014; Shah and Cole, 2010). Cigarette smoking is a risk factor for IS and SAH (Goldstein et al., 2011; Meschia et al., 2014; Shah and Cole, 2010), and at a lower level for primary ICH (O'Donnell et al., 2010). The nicotine and carbon monoxide in cigarette smoke damage the cardiovascular system and pave the way for a stroke to occur.

Smoking may impact the effect of other stroke risk factors on stroke risk. For example, a synergistic effect appears to exist between SBP (Nakamura et al., 2008) and oral contraceptives (WHO, 1996; Xu et al., 2015) and the risk of stroke.

Smoking is perhaps the most important modifiable risk factor in preventing SAH, with the highest population attributable risk of any SAH risk factor (Kissela et al., 2002).

In a large Danish cohort study, among people with AF, smoking was associated with a higher risk of IS/arterial thromboembolism or death, even after adjustment for other traditional risk factors (Albertsen et al., 2014).

Data support a dose-response relationship between smoking and risk of stroke across old and young age groups (Bhat et al., 2008; Goldstein et al., 2011).

A meta-analysis comparing pooled data of ≈3.8 million smokers and nonsmokers found a similar risk of stroke associated with current smoking in women and men (Peters et al., 2013).

Discontinuation of smoking has been shown to reduce stroke risk across sex, race, and age groups (Bhat et al., 2008).

Exposure to second-hand smoke, also termed passive smoking or environmental tobacco smoke, is a risk factor for stroke. Meta-analyses have estimated a pooled RR of 1.25 for exposure to spousal smoking (or nearest equivalent) and risk of stroke. A dose-response relationship between exposure to secondhand smoke and stroke risk was also reported (Lee and Forey, 2006; Oono et al., 2011). Data from another study support these findings; after adjustment for other stroke risk factors, the risk of overall stroke was increased 30% among non-smokers who had secondhand smoke exposure during adulthood (95% CI, 2%–67%) (Malek et al., 2015). Data from another large-scale prospective cohort study of women in Japan showed that environmental tobacco smoke exposure at home during adulthood was associated with an increased risk of stroke mortality in those aged ≥ 80 years (HR, 1.24; 95% CI, 1.05–1.46). Overall, the increased risk was most evident for SAH (HR, 1.66; 95% CI, 1.02–2.70) in all age groups (Nishino et al., 2014).

Waterpipe smokers have increased risk of heart disease and stroke. Waterpipe tobacco and smoke contain many toxic agents that can cause clogged arteries and heart disease (CDC). In a population-based case-control study, Waterpipe smoke was not associated with stroke-related death risk (Mateen et al., 2012).

1.4.1.3 Diabetes

DM is defined as those whose fasting glucose is ≥ 126 mg/dL. Prediabetes is a fasting blood glucose of 100 to <126 mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance. HbA1c levels $\geq 6.5\%$ can be used to diagnose DM (ADA, 2010).

Prediabetes, defined as impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance, may be associated with a higher future risk of stroke, but the RRs are modest. A meta-analysis of 15 prospective cohort studies including 760 925 participants revealed that when prediabetes was defined as fasting glucose 110 to 125 mg/dL (5 studies), the adjusted RR for stroke was 1.21 (95% CI, 1.02–1.44; $P=0.03$) (Lee et al., 2012).

DM is an independent and major risk factor for CVD, such as coronary heart disease (CHD), stroke, peripheral artery disease, heart failure, and AF (Fox et al., 2015).

Self-reported history of DM was associated with an increased risk of all stroke (OR=1.36, 99% CI=1.10–1.68) and IS (OR=1.60, 99% CI=1.29–1.99), but not ICH stroke (OR=0.87, 99% CI=0.60–1.24) (O'Donnell et al., 2010).

The duration of diabetes is also correlated with the risk of IS: each year of diabetes increases the risk by 3% (HR, 1.03, 95% CI, 1.02–1.04) which will be triple after 10 years of illness (HR, 3.2, 95% CI, 2.4–4.5) (Banerjee et al., 2012). A prospective study has shown that for blood glucose values ≥ 110 mg/dL, each 10mg/dL increase is accompanied by an increased risk of stroke of 6% (95% CI, 0-12%, $p=0.05$) (Sui et al., 2011).

DM increases IS incidence at all ages, but this risk is most prominent (risk ratio for IS conferred by DM >5) before 65 years of age in both blacks and whites (Khoury et al., 2013; Kissela et al., 2005). Overall, IS patients with DM are younger, more likely to be black, and more likely to have HBP, MI, and high cholesterol than nondiabetic patients (Khoury et al., 2013).

The association between DM and stroke risk differs between sexes. A systematic review of 64 cohort studies representing 775 385 individuals and 12 539 strokes revealed that the pooled fully adjusted RR of stroke associated with DM was 2.28 (95% CI 1.93–2.69) in women and 1.83 (1.60–2.08) in men. Compared with men with DM, women with DM had a 27% greater RR for stroke when baseline differences in other major cardiovascular risk factors were taken into account (pooled RR, 1.27; 95% CI, 1.10–1.46) (Peters et al., 2014).

DM is an independent risk factor for stroke recurrence; a meta-analysis of 18 studies involving 43 899 participants with prior stroke revealed higher stroke recurrence in patients with DM than in those without (HR, 1.45; 95% CI, 1.32–1.59) (Shou et al., 2015).

A population-based study of 1375 first-ever stroke patients 25 to 74 years old who were followed up for 23 years found that diabetic patients had a higher risk of death than nondiabetic patients (adjusted HR, 1.67; 95% CI, 1.58–1.76). The reduced survival of diabetic stroke patients was more pronounced in women ($P=0.02$) and younger individuals ($P<0.001$) (Eriksson et al., 2012).

Data from the US revealed that from 1997 to 2006, the absolute number of AIS hospitalizations declined by 17%; however, the absolute number of AIS hospitalizations with comorbid DM rose by 27% (from 97 577 [20%] to 124 244 [30%]). Factors independently associated with higher odds of DM in AIS patients were black or “other” (versus white) race, congestive heart

failure, peripheral vascular disease, and history of MI, renal disease, or hypertension (Towfighi et al., 2012).

A study showed that in patients with type 2 DM, targeting SBP to <120 mm Hg did not reduce the rate of cardiovascular events compared with subjects in whom the SBP target was <140 mm Hg, except for the end point of stroke, for which intensive therapy reduced the risk of any stroke (HR, 0.59; 95% CI, 0.39–0.89) and nonfatal stroke (HR, 0.63; 95% CI, 0.41–0.96) (Cushman et al., 2010).

1.4.1.4 Diet

Diets high in saturated fat, trans fat and cholesterol can raise blood cholesterol levels. Diets high in sodium (salt) can increase BP. Diets with high calories can lead to obesity. According to registry data from Sweden, people eating ≥ 7 servings of fruits and vegetables per day had a 19% reduced risk of stroke compared with those only eating 1 serving per day (Larsson et al., 2013). A meta-analysis of 8 prospective studies Larsson et al., 2013 (n=468 887) revealed that a diet containing greater amounts of legumes was not associated with a lower risk of stroke (Shi et al., 2014). Increased consumption of fruit (OR=0.61, 99% CI=0.50–0.73) and fish (OR=0.78, 99% CI=0.66–0.91), but not vegetables (OR=0.91, 99% CI=0.75–1.10), was associated with reduced risk. Increased risk of stroke was associated with: increased consumption of red meat, organ meats, or eggs (OR=1.35, 99% CI=1.10–1.65); increased consumption of fried foods, pizza, or salty snacks (OR=1.16, 99% CI=0.99–1.37); and cooking with lard (OR=1.66, 99% CI=1.06–2.60) (O'Donnell et al., 2010).

A meta-analysis of >94 000 people with 34 817 stroke events demonstrated that eating ≥ 5 servings of fish per week versus eating <1 serving per week was associated with a 12% reduction in stroke risk; however, these results were not consistent across all cohort studies (Chowdhury et al., 2012).

Adherence to a Mediterranean-style diet that was higher in nuts and olive oil was associated with a reduced risk of stroke (diet with nuts: HR, 0.54; 95% CI, 0.35–0.84; diet with olive oil: HR, 0.67; 95% CI, 0.46–0.98; Mediterranean diets combined versus control: HR, 0.61; 95% CI, 0.44–0.86) in a randomized control trial (RCT) conducted in Spain. The protective benefit of the Mediterranean diet observed was greater for strokes than for MI, but stroke subtype was not available (Estruch et al., 2013). A meta-analysis of case-control, prospective cohort studies and an RCT investigating the association between olive oil consumption and the risk of stroke (38 673 participants) revealed a reduction in stroke risk (RR, 0.74; 95% CI, 0.60–0.92) (Martínez-González et al., 2014). A meta-analysis of 20 prospective cohort studies of the

association between nut consumption and cardiovascular outcomes (n=467 389) revealed no association between nut consumption and stroke (2 studies; RR, 1.05; 95% CI, 0.69–1.61) but did find an association with stroke mortality (3 studies; RR, 0.83; 95% CI, 0.69–1.00) (Mayhew et al., 2016). Another meta-analysis of 8 prospective studies (n=468 887) revealed that a diet with greater amounts of nuts was associated with lower risk of stroke (summary RR, 0.90; 95% CI, 0.81–0.99). Sex significantly modified the effects of nut consumption on stroke risk, and high nut intake was associated with reduced risk of stroke in women (SRR, 0.85; 95% CI, 0.75–0.97) but not in men (SRR, 0.95; 95% CI, 0.82–1.11) (Shi et al., 2014).

A meta-analysis of 8 prospective studies (n=410 921) revealed no significant association between consumption of refined grains and risk of stroke (Wu et al., 2015).

A meta-analysis of 10 prospective cohort studies including 314 511 non-overlapping individuals revealed that higher monounsaturated fatty acid intake was not associated with risk of overall stroke (RR, 0.86; 95% CI, 0.74–1.00) and risk of IS (RR, 0.92; 95% CI, 0.79–1.08) but was associated with a reduced risk of hemorrhagic stroke (RR, 0.68; 95% CI, 0.49–0.96) (Cheng et al., 2016).

In the Nurses Health and Health Professionals Follow-up Studies, each 1-serving increase in sugar-sweetened soda beverage was associated with a 13% increased risk of IS but not hemorrhagic stroke. Conversely, each 1-serving increase in low-calorie or diet soda was associated with a 7% increased risk of IS and 27% increased risk of hemorrhagic stroke (Bernstein et al., 2012).

A meta-analysis of prospective cohort studies evaluating the impact of dairy intake on CVD noted that total dairy intake and calcium from dairy were associated with an inverse summary RR estimate for stroke (0.91, 95% CI=0.83–0.99 and 0.69, 95% CI=0.60–0.81) (Alexander et al., 2016). A meta-analysis of 21 studies (n=13 033) evaluating the effect of vitamin D on cardiovascular outcomes revealed that vitamin D supplementation was not associated with a lower risk of stroke (HR, 1.07; 95% CI, 0.91–1.29) (Ford et al., 2014).

A meta-analysis of 14 cohorts (n=333 250) revealed that potassium intake is associated with a lower risk of stroke (RR, 0.80; 95% CI, 0.72–0.90). In addition, the dose-response analysis showed that for every 1 g per day (25.6 mmol per day) increase in vitamin K intake, there was a 10% reduction in stroke risk (RR, 0.90; 95% CI, 0.84–0.96) (D'Elia et al., 2014).

A meta-analysis of 8 studies (n=280 174) indicated an inverse association between flavonol intake and stroke (summary RR, 0.86; 95% CI, 0.75–0.99). An increase in flavonol intake of 20 mg per day was associated with a 14% decrease in the risk for developing stroke (summary RR, 0.86; 95% CI, 0.77–0.96). Subgroup analyses suggested an inverse association between highest flavonol intake and stroke risk among men (summary RR, 0.74; 95% CI, 0.56–0.97) but not women (summary RR, 0.99; 95% CI, 0.85–1.16) (Wang et al., 2014).

In a population of Chinese adults, folate therapy combined with enalapril was associated with a significant reduction in IS risk (HR, 0.76; 95% CI, 0.64–0.91). Although the US population is not as likely to be at risk of folate deficiency because of folate fortification of grains, this study demonstrated the importance of adequate folate levels for stroke prevention (Huo et al., 2015).

1.4.1.5 Physical activity

Physical inactivity can increase stroke risk, HD, becoming overweight, developing HBP, high blood cholesterol and diabetes (Willey et al., 2017). Regular physical activity (PA) was associated with a reduced risk of all stroke (O'Donnell et al., 2010). Over a mean follow-up of 17 years, the ARIC study found a significant trend among African-Americans toward reduced incidence of stroke with increasing level of PA; a similar trend was observed for whites in the study, although it was not statistically significant. Data from this study showed that although the highest levels of activity were most protective, even modest levels of PA appeared to be beneficial (Bell et al., 2013).

A study found that participants reporting PA <4 times per week had a 20% increased risk of incident stroke over a mean of 5.7 years compared with those exercising ≥ 4 times per week. This relationship, which was more pronounced in men than in women, could be explained in large part by the effect of PA on reducing traditional risk factors, such as obesity and DM (McDonnell et al., 2013).

In a prospective cohort that included white, black, and Hispanic adults in an urban setting followed up for a median of 9 years, moderate to vigorous leisure-time PA was associated with an overall 35% reduction in risk of IS (Willey et al., 2009).

In the Aerobics Center Longitudinal Study including 46 405 men and 15 282 women, investigators found that cardiorespiratory fitness as measured by exercise treadmill testing was associated with a reduced risk of fatal and nonfatal stroke. Investigators noted that the effect

was mainly notable for a higher intensity level of fitness achieved (7 to 8 maximum metabolic equivalents) (Hooker et al., 2008). A prospective cohort study of 22 841 men and 24 880 women in Finland found a similar dose-response-independent protective effect from vigorous leisure-time PA on IS, ICH, and SAH. The effect was more modest for commuting-time PA and was no longer present after adjustment for leisure-time PA (Hu et al., 2005).

A dose-response effect was seen for total number of hours spent walking per week, and increased walking time was associated with reduced risk of incident stroke among 4000 men in the British Regional Heart Study. Those reporting ≥ 22 hours of walking per week had one third the risk of incident stroke as those who walked < 4 hours per week. No clear association between walking speed or distance walked was seen in this study (Jefferis et al., 2014).

Timing of PA in relation to stroke onset has also been examined in several studies. In a hospital-based case-control study from Germany, recent activity (within the prior months) was associated with reduced odds of having a stroke or TIA, whereas sports activity during young adulthood that was not continued into adulthood showed no benefit (Grau et al., 2009). In a Danish case-control study, IS patients were less physically active in the week preceding the stroke than age- and sex-matched control subjects, with the highest activity scores associated with the greatest reduction in odds of stroke (Krarup et al., 2007).

Several recent prospective studies found associations of PA and stroke risk in women. In a prospective cohort study among women in England and Scotland, over an average follow-up of 9 years, self-report of any PA at baseline was associated with reduced risk of any stroke, as well as stroke subtypes; however, more frequent or strenuous activity was not associated with increased protection against stroke (Armstrong et al., 2015). Similarly, a low level of leisure-time PA was associated with a 1.5 times higher risk of stroke and a nearly 2.5 times higher risk of fatal stroke than intermediate to high levels of activity in a cohort of ≈ 1500 women followed up for up to 32 years (Blomstrand et al., 2014). A cohort of 25 000 men and women identifying stroke outcomes over a mean of 13 years of follow-up found that among women, participation in any level of PA was associated with a nearly 50% reduction in stroke risk compared with inactivity; no similar pattern was seen for men (Tikk et al., 2014).

1.4.1.6 Obesity

Overweight and obesity in adults is defined as body mass index (BMI) ≥ 25 kg/m². Obesity in adults is defined as BMI ≥ 30 kg/m². For adults, National Heart, Lung and Blood Institute weight

categories are as follows: overweight ($25.0 \leq \text{BMI} \leq 29.9 \text{ kg/m}^2$), and obese class I (BMI 30–35 kg/m^2), class II (BMI >35 to 39.9 kg/m^2), and class III (BMI $\geq 40 \text{ kg/m}^2$) (NHLBI, 2000).

Overweight and obesity are major risk factors for CVD, including CHD, stroke, type 2 DM, hypertension, dyslipidemia, AF (Goldstein et al., 2011; Klein et al., 2004; Poirier et al., 2006; Suk et al., 2003).

1.4.1.7 High blood cholesterol

People with high blood cholesterol have an increased risk for stroke. Large amounts of cholesterol in the blood can build up and cause blood clots, leading to a stroke. Also, it appears that low HDL-C is a risk factor for stroke in men, but more data is needed to verify if this is true for women as well. (AHA/ASA, Stroke Association)

Overall, the association of each cholesterol subfraction with total stroke has shown inconsistent results, and the data are limited on associations with specific IS subtypes. Further research is needed to identify the association of cholesterol with IS subtypes, as well as the association of lobar versus deep ICH (Amarenco et al., 2008; Horenstein et al., 2002; Lewington et al., 2007; Wang et al., 2013; Zhang et al., 2012).

An association between total cholesterol (TC) and IS has been found in some prospective studies (Kurth et al., 2007; Tirschwell et al., 2004; Wang et al., 2013) but not others (Amarenco et al., 2008; Zhang et al., 2012). In the Women's Pooling Project, including those <55 years of age without CVD, TC was associated with an increased risk of stroke at the highest quintile (mean cholesterol 7.6 mmol/L) (Horenstein et al., 2002). An association of elevated TC with risk of stroke was noted to be present in those 40 to 49 years old and 50 to 59 years old but not in other age groups in the Prospective Studies Collaboration (Lewington et al., 2007). Elevated TC is inversely associated in multiple studies with hemorrhagic stroke (Wang et al., 2013).

Data from Japan found that in Japanese men 71 to 93 years of age, low concentrations of HDL-C were more likely to be associated with a future risk of thromboembolic stroke than were high concentrations (Wang et al., 2013). However, a meta-analysis of 23 studies performed in the Asia-Pacific Region showed no significant association between low HDL-C and stroke risk, (Huxley et al., 2011) although another meta-analysis without geographic restriction demonstrated a protective association of HDL-C with stroke (Amarenco et al., 2008). A Finnish study of 27 703 men and 30 532 women followed up for >20 years for IS found an independent inverse association of HDL-C with the risks of total and IS in women (Zhang et al., 2012). In

the Cardiovascular Health Studies, higher HDL-C was associated with a lower risk of IS in men but not in women (Psaty et al., 2004).

In the Women's Health Study, LDL-C was associated with an increased risk of stroke, (Kurth et al., 2007) and LDL-C may have a stronger association for large-artery atherosclerotic subtype (Imamura et al., 2009). In a pooled analysis of Cardiovascular Health Studies and ARIC, low LDL-C (<158.8 mg/dL) was associated with an increased risk of ICH (Sturgeon et al., 2007).

Among 13 951 patients in the Copenhagen Heart Study followed up for 33 years for IS, increasing stepwise levels of nonfasting triglycerides were associated with increased risk of IS in both men and women, (Freiberg et al., 2008) although in ARIC and the Physician's Health Study, there was no association (Bowman et al., 2003; Shahar et al., 2003). In the Rotterdam study (n=9068), increasing quartiles of serum triglycerides were associated with a reduced risk of ICH (Wieberdink et al., 2011).

1.4.1.8 Carotid artery disease

A carotid artery narrowed by fatty deposits from atherosclerosis may become blocked by a blood clot. Because they're located so close to the brain, carotid arteries may more easily cause a stroke, but any artery disease may contribute to a stroke (AHA/ASA).

1.4.1.9 Peripheral artery disease

Peripheral artery disease is the narrowing of blood vessels carrying blood to leg and arm muscles caused by atherosclerosis. People with peripheral artery disease have a higher risk of carotid artery disease, which raises their risk of stroke (AHA/ASA).

1.4.1.10 Atrial fibrillation

AF (a heart rhythm disorder) is a powerful risk factor for stroke, independently increasing stroke risks fivefold throughout all ages. The percentage of strokes attributable to AF increases steeply from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age (Wang et al., 2003; Wolf et al., 1991). That's because it causes the heart's upper chambers to beat incorrectly, which can allow the blood pool and clot to travel to the brain and cause a stroke. A resulting clot can travel to the brain and cause a stroke. Also, sleep apnea can be linked to AF and is associated with increased stroke risks (AHA/ASA).

AF was the most common cardiac source of thromboembolism in cases with IS (203, 9%), with regional variation in prevalence: 86 (23%) in high-income countries, 14 (13%) in South America, 16 (7%) in Africa, 41 (6%) in India, and 46 (5%) in south east Asia (O'Donnell et al., 2010). Because AF is often asymptomatic (Page et al., 1994; Strickberger et al., 2005) and likely frequently undetected clinically, (Tayal et al., 2008) the stroke risk attributed to AF may be substantially underestimated (Elijovich et al., 2009). Screening for AF in patients with cryptogenic stroke or TIA by use of outpatient telemetry for 21 to 30 days has resulted in an AF detection rate of 12% to 23% (Elijovich et al., 2009; Flint et al., 2012; Tayal et al., 2008).

Cardiac etiology was associated with an increased risk of IS (OR, 2.74, 99% CI, 2.03–3.72), but not ICH stroke (OR, 0.90, 99% CI, 0.52–1.56) (O'Donnell et al., 2010).

An analysis of patients from the Veterans Administration showed that among patients with device-documented AF, the presence of relatively brief amounts of AF raised the short-term risk of stroke 4- to 5-fold. This risk was highest in the initial 5 to 10 days after the episode of AF and declined rapidly after longer periods (Turakhia et al., 2015).

Important risk factors for stroke in the setting of AF include advancing age, hypertension, HF, DM, previous stroke or TIA, vascular disease, and female sex (Gage et al., 2001; Lip et al., 2010; Olesen et al., 2011). Additional biomarkers, including high levels of troponin and brain natriuretic peptide, increase the risk of stroke in the setting of AF independent of those well-established clinical characteristics (Hijazi et al., 2012).

CHADS₂ and CHA₂DS₂-VASc Score for Stroke Risk Assessment in AF

It is important to determine which patients with AF may benefit from oral anticoagulant (OAC) and possibly aspirin therapy to reduce the risk of stroke. The CHADS₂ score was developed to more accurately predict the risk of stroke in patients with nonrheumatic AF (Gage et al., 2001). The index was derived by combining risk factors from prior studies and then testing their validity in a cohort of 1,773 Medicare-aged patients over 2,121 patient years (Atrial Fibrillation investigators, 1994; Stroke Prevention Atrial Fibrillation III Writing Committee, 1998) (**Tables 3,4**).

Table 2 CHADS₂ Score: Stroke Risk Assessment in Atrial Fibrillation

CHADS₂ Risk Criteria	Score
Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	1 point

Diabetes mellitus	1 point
Stroke/ transient ischemic attack	2 points

Table 3 CHADS₂ Score and Corresponding Annual Stroke Risk

CHADS ₂ Score	Adjusted Stroke Risk (%)
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

Although simple, the CHADS₂ score does not include many common stroke risk factors, and its limitations have been highlighted by its non-inclusion of common stroke risk factors. Consequently, CHADS₂ was expanded to include three additional independent risk factors: vascular disease (coronary artery disease, peripheral artery disease, aortic atherosclerosis), age 65-74 years, and female sex (Friberg et al., 2012; Olesen et al., 2012; van Walraven et al., 2009). This new, more inclusive scoring system is the CHA₂DS₂-VASc score (Camm et al., 2012) (Tables 5-7).

Table 4 CHA₂DS₂-VASc Score and Risk Criteria

CHA ₂ DS ₂ -VASc Risk Criteria	Score
Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	2 points
Diabetes mellitus	1 point
Stroke/transient ischemic attack	2 points
Vascular disease (prior MI, PAD, or aortic plaque)	1 point
Age 65 to 74 years	1 point
Sex category (ie, female sex)	1 point

Table 5 CHA₂DS₂-VASc Score and Corresponding Annual Stroke Risk

CHA ₂ DS ₂ -VASc Score	Adjusted Stroke Risk (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Table 6 Treatment Recommendations Based on CHA₂DS₂-VASc Score (January et al., 2014)

CHA₂DS₂-VASc Score	Recommendation
0 (Low risk)	None
1 (Moderate risk)	None or aspirin or OAC
2 or more (High risk)	OAC

HAS-BLED

HAS-BLED is a scoring system developed to assess 1-year risk of major bleeding in patients taking anticoagulants with AF. It was developed in 2010 with data from 3,978 patients in the Euro Heart Survey (Pisters et al., 2010). Major bleeding is defined as being intracranial bleedings, hospitalization, hemoglobin decrease > 2 g/dL, and/or transfusion (Pisters et al., 2010). A score of ≥ 3 indicates "high risk" and some caution and regular review of the patient is needed (Lip, 2010) (Tables 8,9).

Table 7 HAS-BLED Bleeding Risk Score

HAS-BLED Bleeding Risk Criteria	Score
Hypertension	1 point
Abnormal liver function	1 point
Abnormal renal function	1 point
Stroke	1 point
Bleeding tendency or predisposition	1 point
Labile INRs in patients taking warfarin	1 point
Elderly: age greater than 65 years	1 point
Drugs: concomitant antiplatelet agent(s) or NSAIDS	1 point
Drugs: alcohol abuse	1 point

Table 8 HAS-BLED Score Interpretation

HAS-BLED Bleeding Risk Score	Risk
0 points	1.13 bleeds per 100 patient-years
1 point	1.02 bleeds per 100 patient-years
2 points	1.88 bleeds per 100 patient-years
3 points	3.74 bleeds per 100 patient-years
4 points	8.70 bleeds per 100 patient-years
5 to 9 points	Insufficient data (high risk)

1.4.1.11 Other heart disease

People who have CHD or heart failure or a prior heart attack are at higher risk of having a stroke than people who have healthy hearts. Dilated cardiomyopathy, heart valve disease and some types of congenital heart defects can also raise the risk of stroke (AHA/ASA).

Left atrial enlargement is associated with AF, causing the 2 conditions to often coexist. A systematic review of 9 cohort studies including 67 875 participants revealed that those with left

atrial enlargement in the setting of sinus rhythm had stroke rates ranging from 0.64 to 2.07 per 100 person-years (Overvad et al., 2016).

1.4.1.12 Sickle cell disease (also called sickle cell anemia)

This treatable genetic disorder mainly affects African-American and Hispanic children. "Sickled" red blood cells are less able to carry oxygen to the body's tissues and organs. These cells also tend to stick to blood vessel walls, which can block arteries to the brain and cause a stroke (AHA/ASA).

1.4.1.13 Metabolic syndrome

Federation, NHLBI, AHA, and others recently proposed a harmonized definition for metabolic syndrome (Alberti et al., 2009). By this definition, metabolic syndrome is diagnosed when any 3 of the following 5 risk factors are present:

- Fasting plasma glucose ≥ 100 mg/dL or undergoing drug treatment for elevated glucose
- HDL-C < 40 mg/dL in males or < 50 mg/dL in females or undergoing drug treatment for reduced HDL-C
- Triglycerides ≥ 150 mg/dL or undergoing drug treatment for elevated triglycerides
- Waist circumference > 102 cm in males or > 88 cm in females for people of most ancestries living in the US. Ethnicity and country-specific thresholds can be used for diagnosis in other groups, particularly Asians and individuals of non-European ancestry who have predominantly resided outside the US.
- BP ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension.

A recent meta-analysis among 87 studies comprising 951 083 subjects showed a higher risk of CVD associated with metabolic syndrome (summary RR, 2.35; 95% CI, 2.02–2.73), with significant increased risks (RRs ranging from 1.6 to 2.9) for all-cause mortality, CVD mortality, MI, and stroke, as well as for those with metabolic syndrome without DM (Mottilo et al., 2010).

1.4.1.14 Chronic Kidney Disease

A meta-analysis of $> 280\,000$ patients showed a 43% increased incident stroke risk among patients with a GFR < 60 mL·min⁻¹·1.73 m⁻² (Lee et al., 2010).

In a study of 539 287 Swedish men and women followed up for 12 years, (Holzmann et al., 2012) HRs for ICH were as follows: for GFR 60 to 90 mL·min⁻¹·1.73 m⁻² (mild), 1.04 (95% CI, 0.93–1.15); for GFR 30 to 60 mL·min⁻¹·1.73 m⁻² (moderate), 1.26 (95% CI, 0.96–1.64); and for GFR 15 to 30 mL·min⁻¹·1.73 m⁻² (severe impairment), 2.31 (95% CI, 1.10–4.87). Among 128 patients with ICH, the presence of GFR <45 mL·min⁻¹·1.73 m⁻² was associated with larger, lobar hematomas and poor outcome (Molshatzki et al., 2011).

A pooled analysis of 4 prospective community-based cohorts including 29 595 participants showed that low estimated GFR (45 mL·min⁻¹·1.73 m⁻²) was significantly associated with increased risk of IS (HR, 1.30; 95% CI, 1.01–1.68) but not hemorrhagic stroke (HR, 0.92; 95% CI, 0.47–1.81) compared with normal GFR (95 mL·min⁻¹·1.73 m⁻²). A high albumin-to-creatinine ratio of 300 mg/g was associated with both IS (HR, 1.62; 95% CI, 1.27–2.07) and hemorrhagic stroke (HR, 2.57; 95% CI, 1.37–4.83) compared with 5 mg/g (Mahmoodi et al., 2014).

Among Scottish stroke patients, 32% of the 2520 stroke patients admitted to 2 teaching hospitals over 3 years had renal dysfunction (estimated GFR <45 mL·min⁻¹·1.73 m⁻²). Stroke patients admitted with renal dysfunction were more likely to die in the hospital (OR, 1.59; 95% CI, 1.26–2.00) (Rowat et al., 2014).

A cohort study found that proteinuria and albuminuria are better predictors of stroke risks than estimated GFR in patients with kidney disease (Sandsmark et al., 2015).

1.4.1.15 Sleep apnea

The Apnea-Hypopnea Index (AHI) is calculated by dividing the number of apnea events by the number of hours of sleep. The AHI values for adults are categorized as (Ruehland et al., 2009):

- Normal: AHI<5
- Mild sleep apnea: 5≤AHI<15
- Moderate sleep apnea: 15≤AHI<30
- Severe sleep apnea: AHI≥30

In a prospective analysis of nationwide databases of the entire Danish population from 2000 to 2011, risk of IS was significantly higher in those with sleep apnea than in the general population (RR, 1.50; 95% CI, 1.35–1.66) (Johnson et al., 2010).

In a meta-analysis of 5 studies, obstructive sleep apnea was associated with incident stroke, with an OR of 2.2 (95% CI, 1.6–3.2). Similar results were found in 2 subsequent meta-analyses

that included additional studies (OR, 2.1; 95% CI, 1.5–2.9 and OR, 2.0; 95% CI, 1.4–2.9) (Dong et al., 2013; Li et al., 2014; Loke et al., 2012).

In the Sleep Heart Health Study, obstructive sleep apnea measured by the obstructive AHI was associated with risk of incident IS in men after adjustment for confounders (P=0.016 for linear trend associated with quartiles of AHI) but not in women. Compared with men in the lowest quartile of AHI (0 to <4.1), men in the highest quartile (AHI >19) had an adjusted HR of 2.9 (95% CI, 1.1–7.4) (Redline et al., 2010).

A study found that acute infarction involving the brainstem (versus no brainstem involvement) was associated with the odds of sleep-disordered breathing, defined as an AHI \geq 10, with an OR of 3.76 (95% CI, 1.44–9.81) after adjustment for demographics, risk factors, and stroke severity (Friberg et al., 2004). In this same study, IS subtype was not found to be associated with the presence or severity of sleep-disordered breathing (Brown et al., 2015).

Moreover, obstructive sleep apnea is common after stroke, with prevalence well in excess of 50% (Broadley et al., 2007; Johnson et al., 2016; Johnson et al., 2010; Lisabeth et al., 2017). Mexican Americans had a higher prevalence of post-stroke sleep-disordered breathing, defined as an AHI \geq 10, than non-Hispanic whites after adjustments for confounders (prevalence ratio, 1.21; 95% CI, 1.01–1.46) (Lisabeth et al., 2017). Obstructive sleep apnea is associated with higher post-stroke mortality (Martínez-García et al., 2009; Parra et al., 2004; Sahlin et al., 2008) and worse functional outcome (Turkington et al., 2002).

No definitive study has been conducted to determine whether treatment with continuous positive airway pressure prevents stroke or improves post-stroke outcomes (Benjamin et al., 2017).

1.4.2. Uncontrollable risk factors

1.4.2.1 Age

People are most likely to have a stroke over the age of 55 (Wang et al., 2013). The likelihood of having a stroke nearly doubles every 10 years after age 55. (Rothwell et al., 2005). Aging has a remarkable effect on the heart and arterial system, leading to an increase in CVD including atherosclerosis, hypertension, MI, and stroke (Lakatta and Levy, 2003 part I). Aging cardiovascular tissues are exemplified by pathological alterations including hypertrophy, altered left ventricular diastolic

function, and diminished left ventricular systolic reverse capacity, increased arterial stiffness, and impaired endothelial function (Lakatta and Levy, 2003 part I & part II]. Aging of the vasculature results in increased arterial thickening and stiffness as well as dysfunctional endothelium. **(Figure 6)** Clinically, these changes result in increased systolic pressure and present major risk factors for development of atherosclerosis, hypertension, stroke, and AF (Lakatta & Levy, 2003 part II).

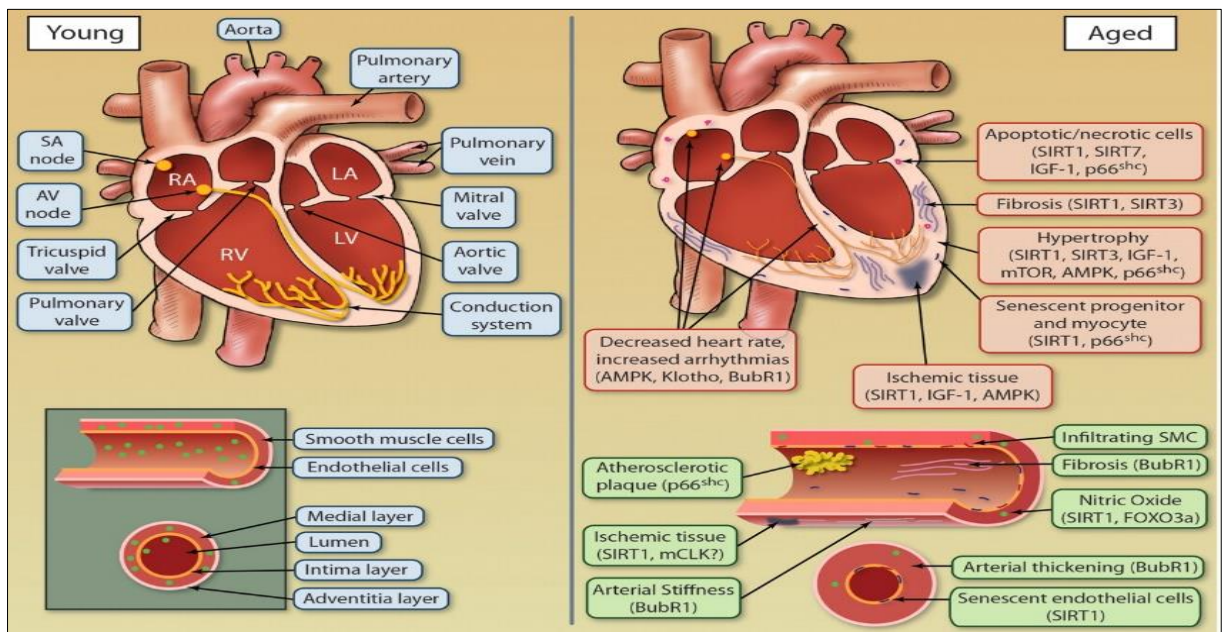


Figure 6 Illustration of cardiovascular tissues aging

Although stroke is more common among the elderly, a lot of people under 65 also have strokes **(Figure 7)**. Around a quarter of strokes happen in people of working age (Stroke Association, 2017). Approximately 10% of all strokes occur in individuals 18 to 50 years of age (Nedelchev et al., 2005). Stroke patients >85 years of age make up 17% of all stroke patients, and in this age group, stroke is more prevalent in women than men (Dehlendorff et al., 2015; Elkind et al., 2016; Russo et al., 2011).

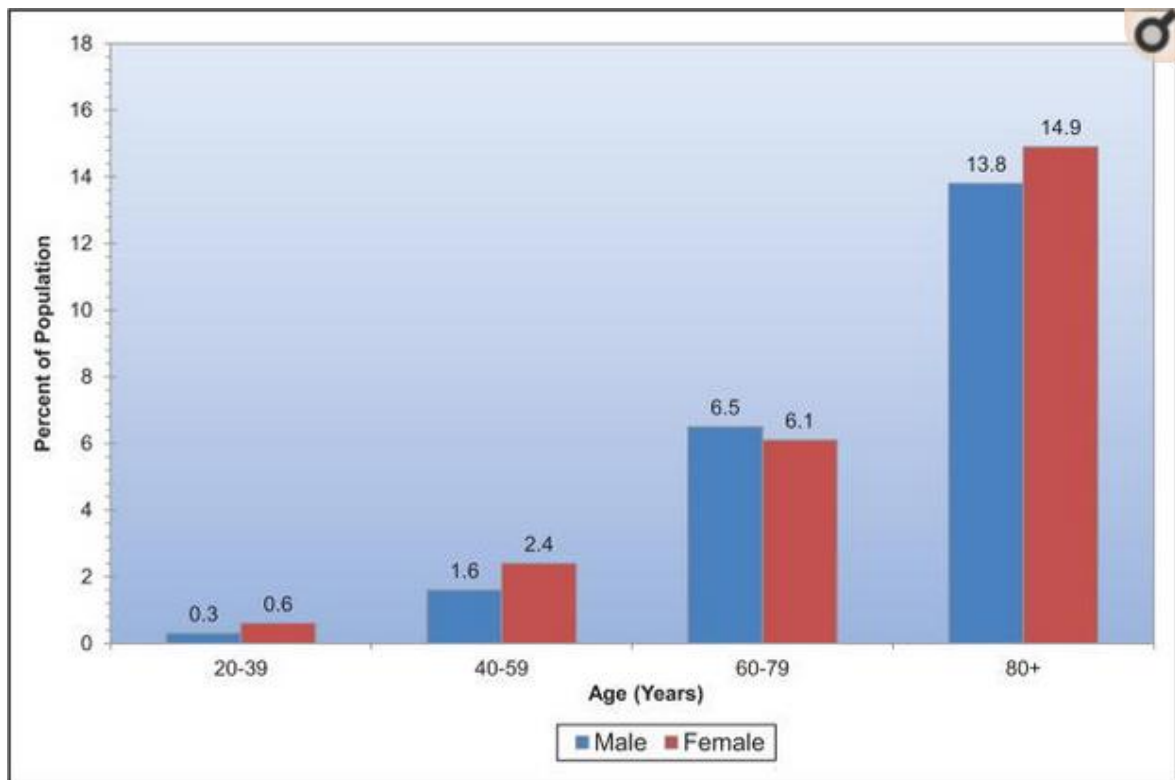


Figure 7 Prevalence of stroke by age and sex (NHANES 2011–2014)

NHANES indicates National Health and Nutrition Examination Survey.

Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

1.4.2.2 Family history of stroke and genetics

IS is a heritable disease; family history of stroke is associated with increased risk of IS, stroke subtypes, and carotid atherosclerosis (Fox et al., 2003). In the Family Heart Study, the adjusted ORs of stroke for a positive paternal and maternal history of stroke were 2.0 and 1.4, respectively, with similar patterns seen in African Americans and European Americans (Liao et al., 1997). In the Framingham study, a documented parental IS by the age of 65 years was associated with a 3-fold increase in IS risk in offspring, even after adjustment for other known stroke risk factors. The absolute magnitude of the increased risk was greatest in those in the highest quintile of the Framingham Stroke Risk Profile. By age 65 years, people in the highest Framingham Stroke Risk Profile quintile with an early parental IS had a 25% risk of stroke compared with a 7.5% risk of IS for those without such a history (Seshadri et al., 2010).

Genetic studies have identified genetic variants associated with risk of ischemic (Flossmann et al., 2004) and ICH stroke (Chauhan and DeBette, 2016). IS and hemorrhagic stroke genes:

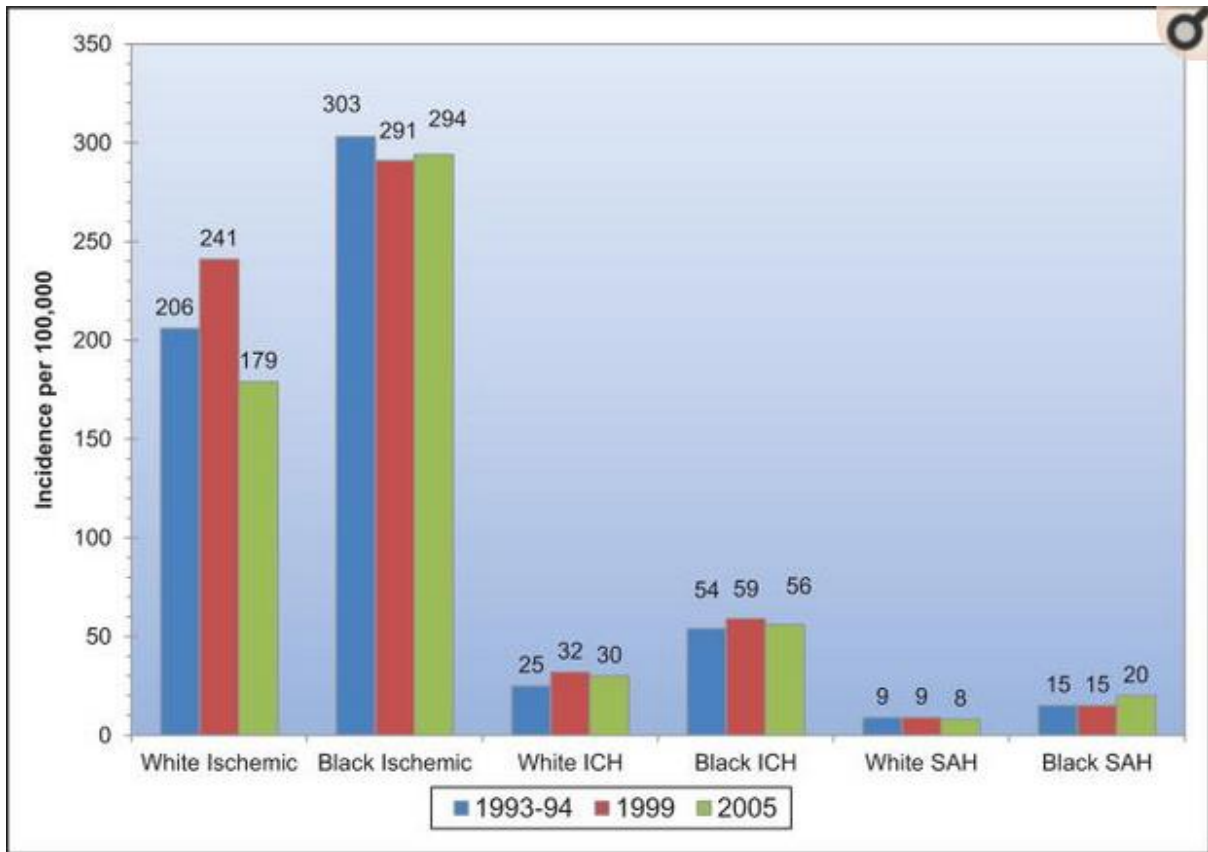
- Gene regions associated at genome-wide levels of significance with large-vessel IS and replicated in independent samples include histone deacetylase 9 on chromosome 7p21.1 (*HDAC*), (ISGC, 2012; Traylor et al., 2012) *ABO*, (Malik et al., 2016; Williams et al., 2013) and *TSPAN2* (SiGN, 2016).
- The 9p21.3 region has been associated with intracranial aneurysm (Foroud et al., 2012) and IS (ISGC, 2012)
- Gene regions associated at genome-wide levels of significance with cardioembolic stroke and replicated in independent samples include *PTX2* (Wu et al., 2007; Bevan et al., 2012) and *ZFHX3* (Gudbjartsson et al., 2009; Traylor et al., 2014). These regions were also identified in GWAS of AF (Gudbjartsson et al., 2009; Gretarsdottir et al., 2008).
- Gene regions associated with small-vessel disease stroke identified by GWAS include *ALDH2/SH2B3* (GBD 2013 Mortality and Causes of Death Collaborators, 2015; Kilarski et al., 2014; SiGN, 2016) and *FOXF2* (Neurology Working Group of the CHARGE SiGN and the ISGC, 2016). Follow-up experimental studies in mouse and zebrafish models of small-vessel disease demonstrated a role of *FOXF2* consistent with a small-vessel disease pathogenesis (Neurology Working Group of the CHARGE SiGN and the ISGC, 2016).
- The *PMF1/BGLAP* region has been associated at a genome-wide level with nonlobar ICH, and this has been replicated in an independent sample (Woo et al., 2014).
- Apolipoprotein E alleles have been associated at a genome-wide level with lobar ICH, and this has been replicated in an independent sample (Biffi et al., 2010).

Recent heritability studies using common genome-wide genotype data have confirmed that genetic susceptibility to IS differs by age and by sex, with a trend toward higher heritabilities in younger cases and in women. Heritability of IS also varies by stroke subtype, with higher estimated heritabilities for large-vessel disease (40.3%) and cardioembolic stroke (32.6%) than for small-vessel disease (16.1%) (Blucher et al., 2015; Traylor et al., 2015; Bevan et al., 2012).

1.4.2.3 Race

Statistics show that African-Americans (Hispanics) have a much higher risk of death from a stroke than Caucasians do (White et al., 2005). The risk of having a first stroke is nearly twice

as high for blacks as for whites (**Figure 8**), (Benjamin et al., 2017) and blacks have the highest rate of death due to stroke (Vital Signs, 2017). This is partly because blacks have higher risks of HBP, diabetes and obesity (Giles et al., 1995). Though stroke death rates have declined for decades among all race/ethnicities, Hispanics have seen an increase in death rates since 2013 (Vital Signs, 2017).



Source: Kleindorfer DO, Khoury J, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Khatri P, Adeoye O, Ferioli S, Broderick JP, Kissela BM. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. *Stroke*. 2010;41:1326–1331.

Figure 8 Annual age-adjusted incidence of first-ever stroke by race

Hospital plus out-of-hospital ascertainment, 1993 to 1994, 1999, and 2005. ICH indicates intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

1.4.2.4 Gender

Women were significantly older at their first-ever stroke, had a higher stroke incidence above 85 years of age, lower at all other ages, and a higher lifetime risk of stroke at all ages (Haast et al., 2012). On average, women are ≈ 4 years older at stroke onset than men (≈ 75 years compared with 71 years) (Kissela et al., 2012). The risk of stroke is increased by 9% per year for men and

10% for women (95% CI, 9-10%) (Asplund et al., 2009). In general, studies show a male/female ratio of 1.55 for IS and 1.60 for ICH. This ratio is 0.84 for SAH, which is more common among women (Appelros et al., 2009). Stroke kills more women than men (Bushnell C et al., 2014).

Factors that may increase stroke risks for women include: pregnancy. (Bushnell C et al., 2014) history of preeclampsia/eclampsia or gestational diabetes, oral contraceptive use (especially when combined with smoking) (Xu et al., 2015) and post-menopausal hormone therapy (Appelros et al., 2009; Baillargeon et al., 2005; Bath and Gray, 2005; Boardman et al., 2015; James et al., 2005).

In the setting of AF, women have a significantly higher risk of stroke than men (Avgil et al., 2005; Dages et al., 2007; Fang et al., 2005; Friberg et al., 2004; Poli et al. 2009).

Analysis of data from the Framingham study found that women with natural menopause before 42 years of age had twice the IS risk of women with natural menopause after 42 years of age; however, no association was found between age at natural menopause and risk of ischemic or hemorrhagic stroke in the Nurse's Health Study (Lisabeth et al., 2009).

Overall, RCT data indicate that the use of estrogen plus progestin, as well as estrogen alone, increases stroke risk in postmenopausal, generally healthy women and provides no protection for postmenopausal women with established CHD (Hendrix et al., 2006; Rossouw et al., 2002; Simon et al., 2001; Wassertheil-Smoller et al., 2003) and recent stroke or TIA (Viscoli et al., 2001). In a nested case-control study in the United Kingdom, stroke risk was not increased for users of low-dose (≤ 50 μg) estrogen patches (RR, 0.81; 95% CI, 0.62–1.05) but was increased for users of high-dose (> 50 μg) patches (RR, 1.89; 95% CI, 1.15–3.11) compared with nonusers (Renoux et al., 2010). Low-estrogen-dose oral contraceptives are associated with a 93% increased risk of IS, but the absolute increased risk is small (4.1 ISs per 100 000 nonsmoking, normotensive women) (Gillum et al., 2000; Gillum and Johnson, 2004; Roach et al., 2015).

Migraine with aura is associated with IS in younger women, particularly if they smoke or use oral contraceptives. The combination of all 3 factors increases the risk ≈ 9 -fold compared with women without any of these factors (MacClellan et al., 2007; Schürks et al., 2009).

In a US study, the risk of IS or ICH during pregnancy and the first 6 weeks after giving birth was 2.4 times greater than for nonpregnant women of similar age and race. The excess risk of stroke (all types except SAH) attributable to the combined pregnancy/postpregnancy period

was 8.1 per 100 000 pregnancies (Kittner et al., 1996). Preeclampsia is a risk factor for IS remote from pregnancy (Kittner et al., 1996). The increase in stroke risk related to preeclampsia may be mediated by later risk of hypertension and DM (Lykke et al., 2009).

1.4.2.5 Prior stroke or TIA

A person who has had a prior stroke has a much higher risk of having another stroke than a person who has never had one. TIAs are also strong predictors of stroke. A person who's had one or more TIAs is almost 10 times more likely to have a stroke than someone of the same age and sex who hasn't. Recognizing and treating TIAs can reduce the risk of a major stroke. TIA should be considered a medical emergency and followed up immediately with a healthcare professional (AHA/ASA).

1.4.3. Additional factors

1.4.3.1 Geographic location

Strokes are more common in the southeastern US than in other areas. These are the so-called "stroke belt" states": North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas (AHA/ASA). Historically, the overall average stroke mortality has been about 30% higher in the stroke belt than in the rest of the nation. The higher stroke risk for the stroke belt compared with other regions does not appear to be attributable to hypertension management, because treatment and control rates were similar for the 2 geographic areas (Howard et al., 2006).

1.4.3.2 Socioeconomic factors

There's some evidence that strokes are more common among those with lower incomes. One reason may be because smoking and obesity rates are also higher. Another reason may be that access to quality healthcare is often more limited at lower income levels (AHA/ASA). People with lower levels of education had higher stroke prevalence (CDC, 2012).

1.4.3.3 Alcohol abuse

Alcohol abuse can lead to medical complications, including stroke. Drinking no more than two drinks per day for men and no more than one drink per day for non-pregnant women lower stroke risk (Zhang et al., 2014). A history of alcohol intake of 1–30 drinks per month was associated with a reduced risk of IS, whereas consumption of more than 30 drinks per month or binge drinking were associated with increased risk compared with never or former alcohol

intake (OR=0.79; 99% CI=0.63–1.00). For ICH stroke, risk increased with alcohol intake (OR=1.41; 99% CI=1.09–1.82) (O'Donnell et al., 2010).

1.4.3.4 Drug abuse

Drug addiction is often a chronic relapsing disorder associated with a number of societal and health-related problems. The most commonly abused drugs, including cocaine, heroin and amphetamines, have been associated with an increased risk of stroke. Strokes caused by drug abuse are often seen in a younger population (AHA/ASA).

1.4.3.5 Sleep habits

Recent studies have begun to clarify the reasons that people who get regular, good quality sleep tend to have lower HD and stroke risks (AHA/ASA). In a recent meta-analysis of 10 studies, a J-shaped relationship was reported between sleep duration and stroke risk, with the lowest risk among those with a sleep duration of 6 to 7 hours per day (Li et al., 2016). In another meta-analysis of 11 studies, long sleep, mostly defined as self-reported sleep of ≥ 8 to 9 hours per night, was associated with incident stroke, with a HR of 1.45 (95% CI, 1.30–1.62) after adjustment for demographics, vascular risk factors, and comorbidities. In this same meta-analysis, short sleep, defined as sleep ≤ 5 to 6 hours per night, was also associated with incident stroke (HR, 1.15; 95% CI, 1.07–1.24) after adjustment for similar factors (Leng et al., 2015).

1.4.3.6 Psychosocial stress and depression

Psychosocial stress was associated with an increased risk of all stroke, with consistent estimates for IS and ICH stroke (OR=1.30; 99% CI=1.06–1.60) (O'Donnell et al., 2010). In another study, higher psychological distress was associated with higher stroke mortality (HR, 1.29; 95% CI, 1.10–1.52) and incident hemorrhagic strokes (HR, 1.70; 95% CI, 1.28–2.25) among 4120 adults after risk adjustment for age, sex, race, and stroke risk factors (Henderson et al., 2013).

Among 6019 adults followed up for a mean of 16.3 years, higher levels of anxiety symptoms were associated with increased risk of incident stroke after adjustment for demographic, cardiovascular, and behavioral risk factors (HR, 1.14; 95% CI, 1.03–1.25). This association remained significant with further adjustment for depressive symptoms (Lambiase et al., 2014).

In the INTERSTROKE study, depression was associated with an increased risk of all stroke (OR=1.35; 99% CI=1.10–1.66) and IS, but not ICH stroke (O'Donnell et al., 2010). In addition, depression was associated with a nearly 2-fold increased odds of stroke after adjustment for

age, socioeconomic status, lifestyle, and physiological risk factors (OR, 1.94; 95% CI, 1.37–2.74) in a cohort of 10 547 Australian women aged 47 to 52 years who were followed up for 12 years (Jackson and Mishra, 2013). In a meta-analysis of 17 community-based or population-based prospective studies published between 1994 and 2010 involving 206 641 participants, people with a history of depression experienced a 34% higher risk for the development of subsequent stroke after adjustment for potential confounding factors (pooled RR, 1.34; 95% CI, 1.17–1.54). Associations were similar for men and women (Dong et al., 2012). Another meta-analysis of 28 prospective cohort studies comprising 317 540 participants with a follow-up period that ranged from 2 to 29 years found that depression was associated with an increased risk of total stroke (pooled HR, 1.45; 95% CI, 1.29–1.63), fatal stroke (pooled HR, 1.55; 95% CI, 1.25–1.93), and IS (pooled HR, 1.25; 95% CI, 1.11–1.40) (Pan et al., 2011).

1.5 Recognizing signs of stroke

Emergency medical services leaders, in coordination with local, regional, and state agencies and in consultation with medical authorities and local experts, should develop triage paradigms and protocols to ensure that patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized instrument for stroke screening, such as the FAST (face, arm, speech test) scale, Los Angeles Prehospital Stroke Screen, or Cincinnati Prehospital Stroke Scale (Class I, LOE B) (Powers et al., 2018).

The FAST test is an easy way to remember and recognize the signs of stroke. FAST is based on the Cincinnati Prehospital Stroke Scale and focuses on 3 symptoms: facial droop (F), arm drift (A) and speech problems (S), with “T” for “time” rounding out the acronym.

The English mass media campaigns ‘Act FAST’ and ‘Be FAST’ aimed to raise stroke awareness and the need to call emergency services at the onset of suspected stroke (**Figures 10,11**).



Figure 9 "Act F.A.S.T." campaign to raise awareness of stroke symptoms and time importance

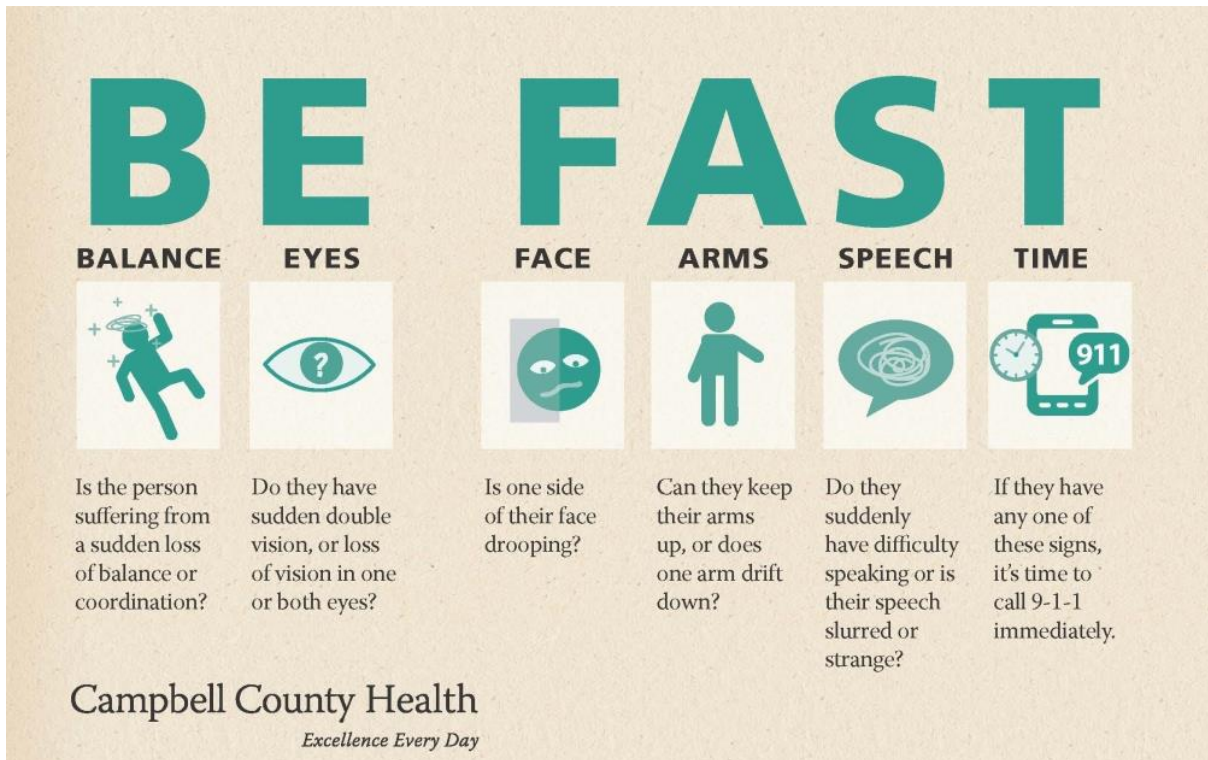


Figure 10 "Be FAST" campaign to raise awareness of stroke symptoms and time importance

Patients with a positive stroke screen and/or a strong suspicion of stroke should be transported rapidly to the closest healthcare facilities that can capably administer IV alteplase (Class I, LOE B) (Powers et al., 2018).

1.6 EARLY MANAGEMENT OF SROKE

1.6.1. Emergency Evaluation and Diagnosis of AIS

The evaluation and initial treatment of patients with stroke should be performed expeditiously. Because time is critical, a limited number of essential diagnostic tests are recommended. Stroke protocols and pathways should clearly define which tests must be performed prior to acute treatment decisions and which may be performed subsequent to acute stroke therapies.

An organized protocol for the emergency evaluation of patients with suspected stroke is recommended. The goal is to complete an evaluation and to begin fibrinolytic treatment within 60 minutes of the patient's arrival in an emergency department. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is encouraged. Patients with stroke should have a careful clinical assessment, including neurological examination (Class I, LOE B) (Powers et al., 2018).

The use of a stroke rating scale, preferably the National Institutes of Health Stroke Scale (NIHSS), is recommended. (Class I, LOE B) (Powers et al., 2018).

Stroke severity (NIHSS)

NIHSS is composed of 11 questions each of which has a specific neurological capacity and whose responses take a score ranging from 0 (normal response) to 2, 3 or 4 (severe dysfunction). The individual scores of each element are summed to give the total NIHSS score. Questions include consciousness level, vision, facial paralysis, motor and limb ataxia, sensitivity, language, extinction, and neglect (**Appendix 2**).

The total score takes a number from 0 to 42:

A score of 1 to 4 indicates a minor stroke.

A score of 5 to 14 indicates a moderate stroke.

A score of 15 to 20 indicates moderate to severe stroke.

A score of 21 to 42 indicates severe stroke.

It is important to assess the severity of stroke as soon as possible after the onset of symptoms to establish the most appropriate treatment (including deciding if the patient is a candidate for thrombolysis) and to judge the effectiveness of this treatment. In addition, the NIHSS predicts the patient's condition after stroke: A score ≤ 6 predicts a good prognosis whereas a score ≥ 16 predicts a high probability of death or severe disability (Adams et al., 1999).

A limited number of hematologic, coagulation, and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of IV rtPA (Class I, LOE B) (Powers et al., 2018).

Baseline electrocardiography assessment is recommended in patients presenting with AIS but should not delay initiation of IV rtPA (Class I, LOE B). Baseline troponin assessment is recommended in patients presenting with AIS but should not delay initiation of IV rtPA (Class I, LOE C) (Powers et al., 2018).

Usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of fibrinolysis (Class IIb, LOE B) (Powers et al., 2018).

1.6.2. Early Diagnosis: Brain and Vascular Imaging

All patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival to hospital. In most cases, noncontrast CT (NCCT) will provide the necessary information to make decisions about acute management (Class I, LOE B) (Powers et al., 2018).

Systems should be established so that brain imaging studies can be performed within 20 minutes of arrival in the emergency department in at least 50% of patients who may be candidates for IV alteplase and/or mechanical thrombectomy (Class I, LOE B) (Powers et al., 2018).

Head CT

- NCCT is excellent in discriminating the presence of an intracranial hemorrhage which will preclude patients from thrombolytics.
- Presence of a hyperdense middle cerebral artery sign is seen in roughly 1/3 of cases but correlates to large vessel occlusion.
- Presence of extensive early ischemic changes on NCCT correlates to an 8-fold risk of symptomatic hemorrhage with IV tPA.

MRI Brain

- Diffusion weighted imaging is highly specific and sensitive in detecting ischemia.
- The gradient recall echo (GRE) sequence may assist in detecting thrombus with higher sensitivity compared to NCCT.
- MR is sensitive at detecting acute hemorrhage and comparable to NCCT and reasonable to use for early imaging.
- Limitations of MR are patient movement, pacemakers, metal implants or claustrophobia.

CT Angiography (CTA)

- The accuracy of CTA for evaluation of large-vessel intracranial stenoses and occlusions is very high.

- Because CTA provides a static image of vascular anatomy, it is inferior to digital subtraction angiography (DSA) for the demonstration of flow rates and direction.
- Direct comparisons of CTA source images and MRI/diffusion weighted imaging (DWI) have demonstrated very similar sensitivity of these two techniques for detecting ischemic regions.

MR Angiography (MRA)

Time of flight MRA is useful in identifying acute proximal large-vessel occlusions but cannot reliably identify distal or branch occlusions.

Transcranial Doppler (TCD)

- TCD accuracy is less compared to CTA and MRA for steno-occlusive disease, with a sensitivity and specificity of TCD ranging from 55-90% and 90-95%, respectively.
- TCD usefulness is limited in patients with poor bony windows, and its overall accuracy is dependent on the experience of the technician, interpreter, and the patient's vascular anatomy.

Conventional Angiography

- DSA remains the "gold standard" for the detection of many types of cerebrovascular lesions and diseases.
- DSA is an invasive test and can cause serious complications such as stroke and death.
- The largest series of cases to date reported a rate of stroke or death of less than 0.2%.
- A CTA or MRA may obviate the need for catheter angiography.

For patients with acute cerebral ischemic symptoms that have not yet resolved

Emergency imaging of the brain is recommended before initiating any specific therapy to treat AIS. In most instances, NCCT will provide the necessary information to make decisions about emergency management (Class I, LOE A). Either NCCT or MRI is recommended before IV rtPA administration to exclude ICH (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present (Class I, LOE A) (Powers et al., 2018).

IV fibrinolytic therapy is recommended in the setting of early ischemic changes on CT (other than frank hypodensity), regardless of their extent (Class I, LOE A). A non-invasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either IA fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay IV rtPA if indicated (Class I, LOE A) (Powers et al., 2018).

In IV fibrinolysis candidates, the brain imaging study should be interpreted within 45 minutes of patient arrival in the emergency department by a physician with expertise in reading CT and MRI studies of the brain parenchyma (Class I, LOE C) (Powers et al., 2018).

CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for selecting patients for acute reperfusion therapy beyond IV fibrinolytic time windows. These techniques provide additional information that may improve diagnosis, mechanism, and severity of IS and allow more informed clinical decision-making (Class IIb, LOE B) (Powers et al., 2018).

Frank hypodensity on NCCT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one third of the middle cerebral artery territory, IV rtPA treatment should be withheld (Class III, LOE A) (Powers et al., 2018).

For patients with acute cerebral ischemic symptoms that have resolved

Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIAs (Class I, LOE A). Noninvasive imaging by means of CTA or MRA of the intracranial vasculature is recommended to exclude the presence of proximal intracranial stenosis and/or occlusion and should be obtained when knowledge of intracranial steno-occlusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with noninvasive testing (Class I, LOE A) (Powers et al., 2018).

Patients with transient ischemic neurologic symptoms should undergo neuroimaging evaluation within 24 hours of symptom onset or as soon as possible in patients with delayed presentations. MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed (Class I, LOE B) (Powers et al., 2018).

1.6.3. General Supportive Care and Treatment of Acute Complications

Cardiac monitoring is recommended to screen for AF and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours (Class I, LOE B). Cardiac arrhythmias that might be reducing cardiac output should be corrected (Class I, LOE C) (Powers et al., 2018).

Blood pressure

Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function (Class I, LOE C). Hypovolemia should be corrected with IV normal saline. (Class I, LOE C) (Powers et al., 2018).

Patients who have elevated BP and are otherwise eligible for treatment of with IV rtPA should have their BP carefully lowered so that their SBP is <185 mm Hg and their DBP is <110 mm Hg before fibrinolytic therapy is initiated. If medications are given to lower BP, the clinician should be sure that the BP is stabilized at the lower level before treating with IV rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after IV rtPA treatment (Class I, LOE B) (Powers et al., 2018).

Restarting antihypertensive medications is relatively safe and reasonable after the first 24 hours for patients who have preexisting hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known (Class IIa, LOE B). No data are available to guide selection of medications for the lowering of BP in the setting of AIS. The antihypertensive medications and doses included in **Table 10** are reasonable choices based on general consensus (Class IIa, LOE C) (Powers et al., 2018).

Table 9 Options to treat arterial hypertension in patients with AIS who are candidates for acute reperfusion therapy*

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/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h
Other agents (eg, hydralazine, enalaprilat) may also be considered
If BP is not maintained \leq 185/110 mmHg, do not administer alteplase

Management of BP during and after alteplase or other acute reperfusion therapy to maintain BP \leq 180/105 mmHg:
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h
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/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h
If BP not controlled or diastolic BP >140 mmHg, consider IV sodium nitroprusside

AIS indicates acute ischemic stroke; BP, blood pressure; IV, intravenous.

*Different treatment options may be appropriate in patients who have comorbid conditions that may benefit from acute reductions in BP such as acute coronary event, acute heart failure, aortic dissection, or preeclampsia/eclampsia.

In patients with markedly elevated BP who do not receive fibrinolysis a reasonable goal is to lower BP by 15% during the first 24 hours after onset of stroke. The level of BP that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the SBP is >220 mm Hg or the DBP is >120 mm Hg (Class I, LOE C) (Powers et al., 2018).

The management of arterial hypertension in patients not undergoing reperfusion strategies remains challenging. Data to guide recommendations for treatment are inconclusive or conflicting. Many patients have spontaneous declines in BP during the first 24 hours after onset of stroke. Until more definitive data are available, the benefit of treating arterial hypertension in the setting of AIS is not well established. Patients who have malignant hypertension or other medical indications for aggressive treatment of PB should be treated accordingly (Class IIb, LOE C) (Powers et al., 2018).

Airway, Breathing, Oxygenation, Temperature and Glycemia

Stroke is a primary failure of focal tissue oxygenation and energy supply. Systemic hypoxemia should be avoided and, if present, corrected to limit further cellular damage.

Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction causing compromise of the airway (Class I, LOE C). Supplemental oxygen should be provided to

maintain oxygen saturation >94% (Class I, LOE C). Supplemental oxygen is not recommended in nonhypoxic patients with AIS (Class III, LOE B) (Powers et al., 2018).

Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Class I, LOE C) (Powers et al., 2018).

Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS. The goal is to achieve normoglycemia (Class I, LOE C). Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia, and thus it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140-180 mg/dL, and to closely monitor to prevent hypoglycemia in patients with AIS (Class IIa, LOE C) (Powers et al., 2018).

1.6.4. Intravenous Fibrinolysis

In the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Trial, treatment with IV rtPA was associated with an increase in the odds of a favorable outcome (OR 1.9; 95% CI 1.2-2.9); the benefit was similar 1 year after stroke. The earlier that treatment is initiated, the better the result.

Early minimal neurologic symptoms or neurologic deterioration temporally associated with any intracranial hemorrhage occurred in 6.4% of patients treated with IV rtPA and 0.6% of patients given placebo; however, mortality in the 2 treatment groups was similar at 3 months (17% versus 20%) (NINDS rtPA Stroke Study Group, 19995).

IV rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of IS (Class I, LOE A). In patients eligible for IV rtPA, benefit of therapy is time-dependent, and treatment should be initiated as quickly as possible. The door to needle time (time of bolus administration) should be within 60 minutes from hospital arrival (Class I, LOE A) (Powers et al., 2018).

In patients undergoing fibrinolytic therapy, physicians should be aware of and prepared to emergently treat potential side effects including bleeding complications and angioedema that may cause partial airway obstruction (Class I, LOE B) (Powers et al., 2018).

IV rtPA is reasonable in patients with a seizure at the time of onset of stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon (Class IIa, LOE C) (Powers et al., 2018).

The effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established (Class IIb, LOE B) (Powers et al., 2018).

The usefulness of IV administration of tenecteplase, reteplase, desmoteplase, urokinase, or other fibrinolytic agents, and the IV administration of ancrod or other defibrinogenating agents is not well established and should only be used in the setting of a clinical trial (Class IIb, LOE B). The IV administration of streptokinase for treatment of stroke is not recommended (Class III, LOE A) (Powers et al., 2018).

The use of IV fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent MI may be considered, and potential increased risk should be weighed against the anticipated benefits. These circumstances require further study (Class IIb, LOE C) (Powers et al., 2018).

The use of IV rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, or TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for more than 2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for IA rtPA (Class III, LOE C) (Powers et al., 2018).

Extended IV rtPA window

European Cooperative Acute Stroke Study III results indicated that IV rtPA can improve outcomes for, carefully selected patients treated 3–4.5 hours after stroke (Hacke et al., 2008).

A meta-analysis of 12 IV rtPA trials confirmed the benefits of IV rtPA administered within 6 hours from symptom onset (OR 1.17, 95% CI 1.06 –1.29; p=0.001) and reinforced the importance of timely treatment because the benefit of IV rtPA is greatest in patients treated within 3 hrs from symptom onset (Wardlaw et al., 2012).

Health systems should set a goal of increasing their percentage of stroke patients treated within 60 minutes of presentation to hospital (door to needle time of 60 minutes) to at least 80% (Powers et al., 2018).

IV rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3–4.5 hours after stroke onset. The eligibility criteria for treatment in this time period are similar to those for persons treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients older than 80 years, those taking oral anticoagulants regardless of INR, those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one-third of the middle cerebral artery territory, or those with both a history of stroke and diabetes (Class I, LOE B) (Powers et al., 2018).

For patients who can be treated in the time period of 3–4.5 hours after stroke but have one or more of the following exclusion criteria: 1) patients older than 80 years, 2) those taking oral anticoagulants, even with $\text{INR} \leq 1.7$, 3) those with a baseline NIHSS >25, or 4) those with both a history of both stroke and diabetes, the effectiveness of IV treatment with rtPA is not well-established, and requires further study (Class IIb, LOE C) (Powers et al., 2018).

1.6.5. Endovascular Interventions

IA fibrinolysis or mechanical thrombectomy are reasonable in patients who have contraindications to the use of IV fibrinolysis (Class IIa, LOE C) (Powers et al., 2018).

Rescue IA fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large artery occlusion who have not responded to IV fibrinolysis. Additional randomized trial data are needed (Class IIb, LOE B) (Powers et al., 2018).

• Intra-Arterial Fibrinolysis

– Prolyse in Acute Cerebral Thromboembolism II study showed a 15% absolute difference in good outcome favoring IA pro-urokinase ($p < 0.04$) (del Zoppo et al., 1998).

– Middle cerebral artery Embolism Local fibrinolytic intervention Trial terminated early but showed for mRS 0-1 better outcomes compared to control (Abou-Chebl, 2011).

Patients eligible for IV rtPA should receive IV rtPA even if IA treatments are being considered (Class I, LOE A) (Powers et al., 2018).

Results of IA fibrinolysis are likely dependent on efficient and timely systems based approach similar to IV tPA. IA fibrinolysis is beneficial for treatment of carefully selected patients with major ISs of <6 hours duration due to occlusions of the middle cerebral artery, who are not otherwise candidates for IV rtPA. As with IV fibrinolytic therapy, reduced time from symptom

onset to reperfusion with intra-arterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy. The optimal dose of IA rtPA remains is not well established and does not have Food and Drug Administration approval for IA use (Class I, LOE B) (Powers et al., 2018).

IA treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria to credential individuals who can perform IA revascularization procedures. Outcomes on all patients should be tracked (Class I, LOE C) (Powers et al., 2018).

- *Mechanical Clot Disruption/Extraction*

Recanalization by mechanical thrombectomy may occur due to a combination of thrombus fragmentation, thrombus retrieval, and enhancement of fibrinolytic penetration. There are currently four devices cleared by the Food and Drug Administration for recanalization of arterial occlusion in patients with IS (Merci, Penumbra, Solitaire, Trevo). When mechanical thrombectomy is pursued, stent retrievers, such as Solitaire FR and Trevo, are generally preferred to coil retrievers such as Merci. The relative effectiveness of the Penumbra System vs. stent retrievers is not yet characterized (Class I, LOE A) (Powers et al., 2018).

The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients. Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in RCT to determine the efficacy of such treatments in improving patient outcomes (Class IIa, LOE B) (Powers et al., 2018).

The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established. These devices should be used in the setting of clinical trials (Class IIb, LOE C) (Powers et al., 2018).

The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These devices should be used in the setting of clinical trials (Class IIb, LOE C) (Powers et al., 2018).

The usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients is not well established. Use of these techniques may be considered in certain circumstances, such as in the treatment of AIS from cervical atherosclerosis or

dissection. Additional randomized trial data are needed (Class IIb, LOE C) (Powers et al., 2018).

1.6.6. Anticoagulants

The results of several clinical trials demonstrate an increased risk of bleeding complications with early administration of either unfractionated heparin or low molecular weight heparin. Early administration of unfractionated heparin or low molecular weight heparin does not lower the risk of early recurrent stroke, including among persons with cardioembolic sources. The PREVAIL study gives the strongest evidence of the superiority of low molecular weight heparin in prevention of venous thromboembolism following IS (Muir, 2008).

The role of anticoagulants as an adjunct in addition to mechanical or pharmacological fibrinolysis has not been established.

At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with AIS is not well established. These agents should be used in the setting of clinical trials (Class IIb, LOE B) (Powers et al., 2018).

The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an IS is not well established (Class IIb, LOE B) (Powers et al., 2018).

Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after AIS, is not recommended for treatment of patients with AIS (Class III, LOE A) (Powers et al., 2018).

Urgent anticoagulation for the management of noncerebrovascular conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications (Class III, LOE A) (Powers et al., 2018).

Initiation of anticoagulant therapy within 24 hours of treatment with IV rtPA is not recommended (Class III, LOE B) (Powers et al., 2018).

1.6.7. Antiplatelet Agents

Currently available data demonstrate a small but statistically significant decline in mortality and unfavorable outcomes with the administration of aspirin within 48 hours following stroke. Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients (Class I, LOE A).

Aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including IV rtPA (Class III, LOE B).

The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of IV fibrinolysis is not recommended (Class III, LOE C) (Powers et al., 2018).

Data regarding the utility of other antiplatelet agents, including clopidogrel alone or in combination with aspirin, for the treatment of AIS are limited. The usefulness of clopidogrel for the treatment of AIS is not well established. Further research testing the usefulness of the emergency administration of clopidogrel in the treatment of patients with acute stroke is required (Class IIb, LOE C) (Powers et al., 2018).

Research of intravenously administered antiplatelet agents is ongoing. The efficacy of intravenous tirofiban and eptifibatid are not well established and should be used in the setting of clinical trials (Class IIb, LOE C) (Powers et al., 2018).

The administration of other IV antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended. Further research testing the usefulness of emergency administration of these medications as a treatment option in patients with AIS is required (Class III, LOE B) (Powers et al., 2018).

1.6.8. Volume Expansion, Vasodilators, and Induced Hypertension

The usefulness of drug-induced hypertension in patients with AIS is not well established. Induced hypertension should be performed in the setting of clinical trials (Class IIb, LOE B). In exceptional cases with systemic hypotension producing neurologic sequelae, a physician may prescribe vasopressors to improve cerebral blood flow. If drug-induced hypertension is used, close neurological and cardiac monitoring is recommended (Class I, LOE C) (Powers et al., 2018).

The administration of high dose albumin is not well established as a treatment for most patients with AIS until further definitive evidence regarding efficacy becomes available (Class IIb, LOE B) (Powers et al., 2018).

At present, use of devices to augment cerebral blood flow for the treatment of patients with AIS is not well established. These devices should be used in the setting of clinical trials (Class IIb, LOE B) (Powers et al., 2018).

Hemodilution by volume expansion is not recommended for treatment of patients with AIS (Class III, LOE A) (Powers et al., 2018).

The administration of vasodilatory agents, such as pentoxifylline, is not recommended for treatment of patients with AIS (Class III, LOE A) (Powers et al., 2018).

1.6.9. Neuroprotective agents

Among patients already taking statins at the time of onset of IS, continuation of statin therapy during the acute period is reasonable (Class IIa, LOE B) (Powers et al., 2018).

The utility of induced hypothermia for the treatment of patients with IS is not well established, and further trials are recommended (Class IIb, LOE B) (Powers et al., 2018).

At present, transcranial near-infrared laser therapy is not well established for the treatment of AIS, and further trials are recommended (Class IIb, LOE B) (Powers et al., 2018).

At present, no other pharmacologic agents with putative neuroprotective actions have demonstrated efficacy in improving outcomes after IS, and therefore other neuroprotective agents are not recommended (Class III, LOE A) (Powers et al., 2018).

Data on the utility of hyperbaric oxygen are inconclusive, and some data imply that the intervention may be harmful. Thus, with the exception of stroke secondary to air embolization, this intervention is not recommended for treatment of patients with AIS (Class III, LOE B) (Powers et al., 2018).

1.6.10. Surgical Interventions

Emergent carotid endarterectomy and other operations for treatment of patients with AIS may have serious risks and the indications must be considered carefully for each individual patient. Additional RCTs should be designed and undertaken to examine the safety and efficacy of carotid endarterectomy in various subsets of patients with acute stroke, to establish the optimal timing for revascularization, and to define its role in the emergency management of stroke (Powers et al., 2018).

The usefulness of emergent or urgent carotid endarterectomy when clinical indicators or brain imaging suggest a small infarct core with large territory at risk (e.g. penumbra), compromised by inadequate flow from a critical carotid stenosis or occlusion, or in the case of acute neurologic deficit after carotid endarterectomy, where acute thrombosis of the surgical site is suspected, is not well established (Class IIb, LOE B) (Powers et al., 2018).

In patients with unstable neurologic status --either stroke-in-evolution or crescendo TIA-- the efficacy of emergent or urgent carotid endarterectomy is not well established (Class IIb, LOE B) (Powers et al., 2018).

1.6.11. Admission to the Hospital and General Acute Treatment (After Hospitalization)

Approximately 25% of patients may have neurological worsening during the first 24 to 48 hours after stroke and it is difficult to predict which patients will deteriorate (Powers et al., 2018).

The importance of dedicated stroke nursing care in the management of stroke patients cannot be overstated. The use of comprehensive specialized stroke care (stroke units) incorporating rehabilitation is recommended (Class I, LOE A). The use of standardized stroke care order sets is recommended to improve general management (Class I, LOE B) (Powers et al., 2018).

Patients with suspected pneumonia or urinary tract infections should be treated with appropriate antibiotics (Class I, LOE A). Routine use of prophylactic antibiotics has not been shown to be beneficial (Class III, LOE B). Routine placement of indwelling bladder catheters is not recommended because of the associated risk of catheter associated urinary tract infections (Class III, LOE C) (Powers et al., 2018).

Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent deep vein thrombosis (Class I, LOE A). The use of aspirin is reasonable for treatment of patients who cannot receive anticoagulants for deep vein thrombosis prophylaxis (Class IIa, LOE A). The use of intermittent external compression devices is reasonable for treatment of patients who cannot receive anticoagulants (Class IIa, LOE B) (Powers et al., 2018).

Assessment of swallowing before starting eating, drinking, or receiving oral medications is recommended (Class I, LOE B). Patients who cannot take solid food and liquids orally should receive nasogastric, nasoduodenal, or percutaneous endoscopic gastrostomy tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing (Class I, LOE B). In selecting between nasogastric versus percutaneous endoscopic gastrostomy tube routes of feeding in patients who cannot take solid food or liquids orally, it is reasonable to prefer nasogastric tube feeding until 2-3 weeks post stroke onset (Class IIa, LOE B) (Powers et al., 2018).

Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended (Class I, LOE C) (Powers et al., 2018).

Treatment of concomitant medical diseases is recommended (Class I, LOE C) (Powers et al., 2018).

Early institution of interventions to prevent recurrent stroke is recommended (Class I, LOE C) (Powers et al., 2018).

1.6.12. Treatment of Acute Neurological Complications

Given the complexity of severe stroke and potential complications, multidisciplinary care teams comprised of neurologists, neurointensivists, and neurosurgeons, as well as dedicated stroke nursing, are required to optimally manage these complex patients.

Patients with major infarctions are at high risk for complicating brain edema and increased intracranial pressure. Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended. Early transfer of patients at risk for malignant brain edema to an institution with neurosurgical expertise should be considered (Class I, LOE A).

Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially life-saving. Advanced patient age and patient/family valuations of achievable outcome states may affect decisions regarding surgery (Class I, LOE B).

Although aggressive medical measures have been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, the usefulness of these measures is not well established (Class IIb, LOE C).

Because of lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) are not recommended for treatment of cerebral edema and increased intracranial pressure complicating IS (Class III, LOE A) (Powers et al., 2018).

Decompressive surgical evacuation of a space occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression (Class I, LOE B) (Powers et al., 2018).

Placement of a ventricular drain is useful in patients with acute hydrocephalus secondary to IS (Class I, LOE C) (Powers et al., 2018).

Recurrent seizures after stroke should be treated in a manner similar to other acute neurological conditions and anti-epileptic agents selected by specific patient characteristics (Class I, LOE B). Prophylactic use of anticonvulsants is not recommended (Class III, LOE C) (Powers et al., 2018).

1.7 Management of Spontaneous Intracerebral Hemorrhage

1.7.1. Prehospital Management

Prehospital management for ICH is similar to that for IS. The primary objective is to provide airway management if needed, provide cardiovascular support, and transport the patient to the closest facility prepared to care for patients with acute stroke (Acker et al., 2007).

Secondary priorities for emergency medical services providers include obtaining a focused history regarding the timing of symptom onset (or the time the patient was last normal); information about medical history, medication, and drug use; and contact information for family. Emergency medical services providers should provide advance notice to the emergency department of the impending arrival of a potential stroke patient so that critical pathways can be initiated and consulting services alerted. Advance notice by emergency medical services has been demonstrated to significantly shorten time to CT scanning in the emergency department (Abdullah et al., 2008).

1.7.2. Emergency Diagnosis and Assessment

ICH is a medical emergency. Rapid diagnosis and attentive management of patients with ICH is crucial, because early deterioration is common in the first few hours after ICH onset.

A baseline severity score should be performed as part of the initial evaluation of patients with ICH (Class I; LOE B) (Hemphill et al., 2015).

Rapid neuroimaging with CT or MRI is recommended to distinguish IS from ICH (Class I; LOE A) (Hemphill et al., 2015). CT is very sensitive for identifying acute hemorrhage and is considered the “gold standard”; MRI is as sensitive as CT for detection of acute hemorrhage and is more sensitive for identification of prior hemorrhage (Chalela et al., 2007; Fiebach et al., 2004).

1.7.3. Medical Treatment for ICH

1.7.3.1 Hemostasis and Coagulopathy, Antiplatelet Agents, and Deep Vein Thrombosis Prophylaxis

Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I; LOE C) (Hemphill et al., 2015).

Patients with ICH whose INR is elevated because of vitamin K antagonist should have their vitamin K antagonist withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K (Class I; LOE C) (Hemphill et al., 2015).

Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission (Class I; LOE A) (Hemphill et al., 2015).

After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset (Class IIb; LOE B) (Hemphill et al., 2015).

1.7.3.2 Blood Pressure

For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class I; LOE A) and can be effective for improving functional outcome (Class IIa; LOE B) (Hemphill et al., 2015).

For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; LOE C) (Hemphill et al., 2015).

1.7.3.3 Glucose Management

Glucose should be monitored. Both hyperglycemia and hypoglycemia should be avoided (Class I; LOE C) (Hemphill et al., 2015).

1.7.4. General Monitoring and Nursing Care

Initial monitoring and management of ICH patients should take place in an intensive care unit or dedicated stroke unit with physician and nursing neuroscience acute care expertise (Class I; LOE B) (Hemphill et al., 2015).

1.7.5. Seizures and Antiseizure Drugs

Clinical seizures should be treated with antiseizure drugs (Class I; LOE A) (Hemphill et al., 2015).

Patients with a change in mental status who are found to have electrographic seizures on electroencephalography should be treated with antiseizure drugs (Class I; LOE C) (Hemphill et al., 2015).

Prophylactic antiseizure medication is not recommended (Class III; LOE B) (Hemphill et al., 2015).

1.7.6. Management of Medical Complications

A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake to reduce the risk of pneumonia (Class I; LOE B) (Hemphill et al., 2015).

Systematic screening for myocardial ischemia or infarction with electrocardiogram and cardiac enzyme testing after ICH is reasonable (Class IIa; LOE C) (Hemphill et al., 2015).

1.7.7. Procedures/Surgery

1.7.7.1 Intracranial Pressure Treatment

Basic principles include elevation of the head of the bed to 30°, the use of mild sedation, and avoidance of collar-endotracheal tube ties that might constrict cervical veins (Wolfe and Torbey, 2009).

Mannitol or hypertonic saline may be used to treat acute intracranial pressure elevations, and hypertonic saline may be more effective (Kamel et al., 2011).

In patients with cerebrospinal fluid outflow obstruction caused by hydrocephalus or a trapped ventricle, cerebrospinal fluid drainage should be considered. Salvage therapies might include barbiturate coma or mild hypothermia.

Ventricular drainage as treatment for hydrocephalus is reasonable, especially in patients with decreased level of consciousness (Class IIa; LOE B) (Hemphill et al., 2015).

Corticosteroids should not be administered for treatment of elevated intracranial pressure in ICH (Class III; LOE B) (Hemphill et al., 2015); they are not effective in ICH and increase complications (Poungvarin et al., 1987).

1.7.7.2 Surgical Treatment of intracranial pressure

Hematoma evacuation and decompressive craniectomy are options for treating elevated intracranial pressure.

Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo

surgical removal of the hemorrhage as soon as possible (Class I; LOE B) (Hemphill et al., 2015).

1.7.8. Prevention of Recurrent ICH

When stratifying a patient's risk for recurrent ICH may affect management decisions, it is reasonable to consider the following risk factors for ICH recurrence: (1) lobar location of the initial ICH; (2) older age; (3) presence and number of microbleeds on gradient echo MRI; (4) ongoing anticoagulation; and (5) presence of apolipoprotein E ϵ 2 or ϵ 4 alleles (Class IIa; LOE B) (Hemphill et al., 2015).

BP should be controlled in all ICH patients (Class I; LOE A). Measures to control BP should begin immediately after ICH onset (Class I; LOE A). A long-term goal of BP <130 mmHg systolic and 80 mmHg diastolic is reasonable (Class IIa; LOE B) (Hemphill et al., 2015).

Lifestyle modifications, including avoidance of alcohol use greater than 2 drinks per day, tobacco use, and illicit drug use, as well as treatment of obstructive sleep apnea, are probably beneficial (Class IIa; LOE B) (Hemphill et al., 2015).

Avoidance of long-term anticoagulation with warfarin as a treatment for nonvalvular AF is probably recommended after warfarin-associated spontaneous lobar ICH because of the relatively high risk of recurrence (Class IIa; LOE B) (Hemphill et al., 2015).

Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents (Class IIb; LOE B) (Hemphill et al., 2015).

The optimal timing to resume oral anticoagulation after anticoagulant-related ICH is uncertain. Avoidance of oral anticoagulation for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence (Class IIb; LOEB) (Hemphill et al., 2015).

If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain (Class IIa; LOE B) (Hemphill et al., 2015).

The usefulness of dabigatran, rivaroxaban, or apixaban in patients with AF and past ICH to decrease the risk of recurrence is uncertain (Class IIb; LOE C) (Hemphill et al., 2015).

There are insufficient data to recommend restrictions on the use of statins in ICH patients (Class IIb; LOE C) (Hemphill et al., 2015).

1.7.9. Rehabilitation and Recovery

Given the potentially serious nature and complex pattern of evolving disability and the increasing evidence for efficacy, it is recommended that all patients with ICH have access to multidisciplinary rehabilitation (Class I; LOE A) (Hemphill et al., 2015).

Where possible, rehabilitation can be beneficial when begun as early as possible and continued in the community as part of a well-coordinated (“seamless”) program of accelerated hospital discharge and home-based resettlement to promote ongoing recovery (Class IIa; LOE B) (Hemphill et al., 2015).

1.8. Global Burden of Stroke

Stroke remains a significant burden across the globe. Although global age-adjusted mortality rates for ischemic and hemorrhagic stroke decreased between 1990 and 2013, the absolute number of people who have strokes annually, as well as related deaths and Disability-Adjusted Life Years (DALY)s lost, increased. The majority of global stroke burden is in low- and middle-income countries (LMIC) (Feigin et al., 2014; Feigin et al., 2015; GBD 2013 Mortality and Causes of Death Collaborators, 2015). On average, stroke occurs 15 years earlier in LMIC when compared to those in high-income countries (HIC) (Owolabi et al., 2009) and 70% of strokes occur in LMIC (Feigin et al., 2014). Data from 2013 indicate that 75.2% of deaths caused by stroke and 81% of DALYs lost as a result of stroke across the globe occur in LMIC too (Feigin et al., 2015).

1.8.1. Stroke Prevalence

- In 2013, there were globally almost 25.7 million stroke survivors (71% with IS), with 10.3 million people having a first stroke (Feigin et al., 2015).
- Approximately 2 of every 3 first strokes were IS (Feigin et al., 2014).
- 5.2 million (31%) first strokes were in those <65 years of age (Feigin et al., 2014).
- Stroke prevalence was 1.47% in Italy, 1.7% in UK and 3% in the USA (Zhang et al., 2012). In China, stroke prevalence varied between 1.8% in the rural areas and 9.4% in the urban areas (Sousa et al., 2009). With the exception of Peru (2.7%), stroke prevalence in Latin America varied between 6 and 8%. In India, the prevalence was quite low and varied between 1 and 2% (Ferri et al., 2011).

- In 2010, the number of cases of stroke in the European Union member states plus Iceland, Norway and Switzerland was estimated to be 8.2 million (Gustavsson et al., 2011).

1.8.2. Stroke Incidence

Over the last four decades, the stroke incidence in LIMC has more than doubled. During these decades stroke incidence has declined by 42% in HIC (Feigin et al., 2014).

Incidence rates for stroke ranged from 41 per 100 000 population per year in Nigeria (1971–74) to 316 per 100 000 per year in urban Dar-es-Salaam (Tanzania), when adjusted to the WHO world standard population. Some regions had three to fivefold greater incidence than other countries (Thrift et al., 2014) (Figures 11,12).

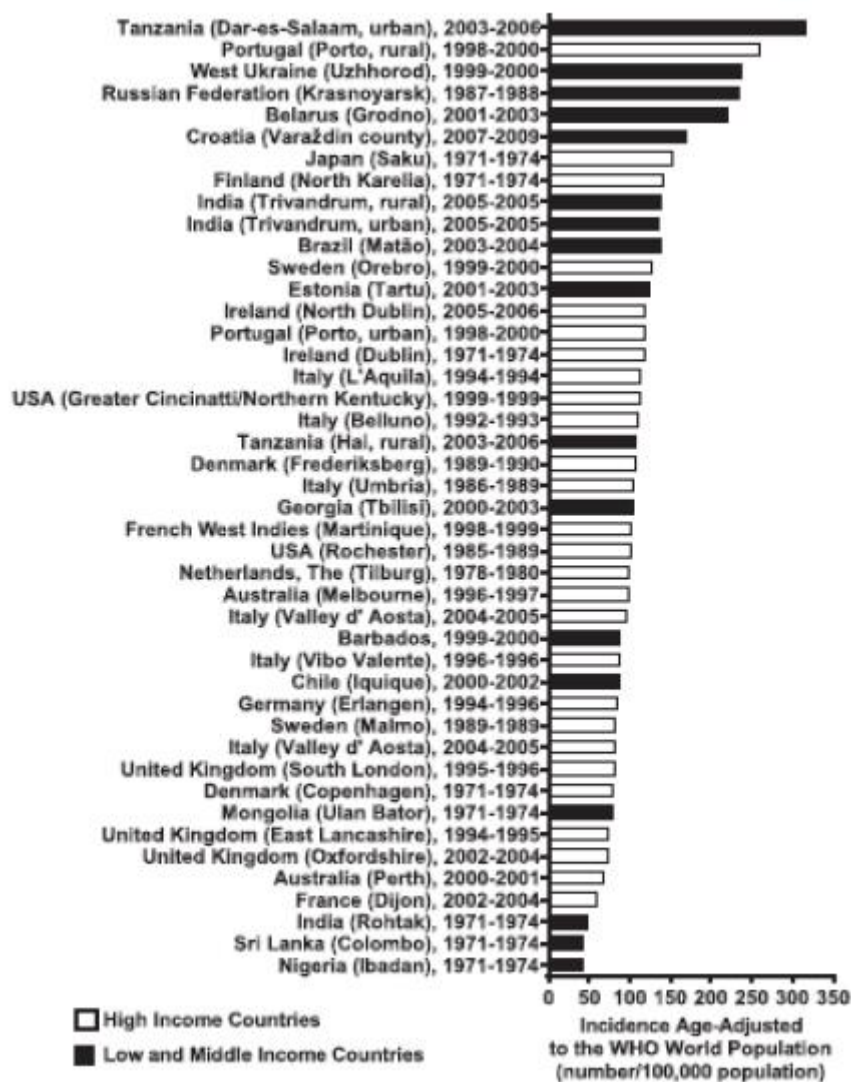


Figure 11 Stroke incidence age-adjusted to the WHO World Population

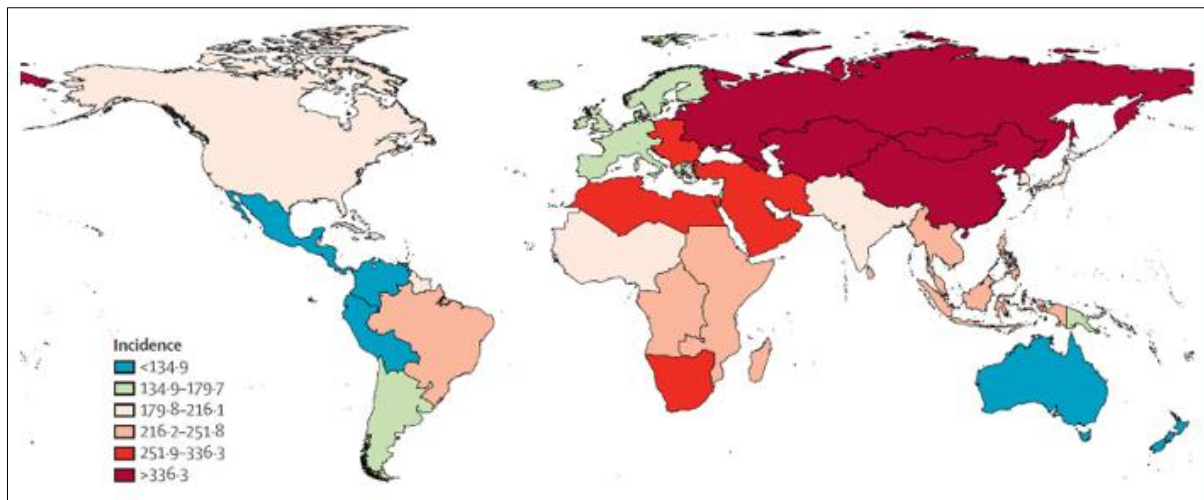


Figure 12 Stroke incidence in the world (per 100,000 person-years) (Feigin et al., 2014)

In 2013, there were globally 10.3 million new strokes (67% IS) (Feigin et al., 2015).

In 2010, there were an estimated 11.6 million events of incident IS and 5.3 million events of incident hemorrhagic stroke, 63% and 80%, respectively, in LIMC (Krishnamurthi et al., 2013). Between 1990 and 2010 (Krishnamurthi et al., 2013):

- Incidence of IS was significantly reduced by 13% (95% CI, 6%–18%) in HIC. No significant change was seen in LIMC.
- Incidence of hemorrhagic stroke decreased by 19% in HIC. Rates increased by 22% in LIMC, with a 19% increase in those aged <75 years.

In developed countries, the incidence of stroke is declining, largely due to efforts to lower BP and reduce smoking. However, the overall rate of stroke remains high due to the aging of the population (Stroke statistics).

1.8.3. Stroke Mortality

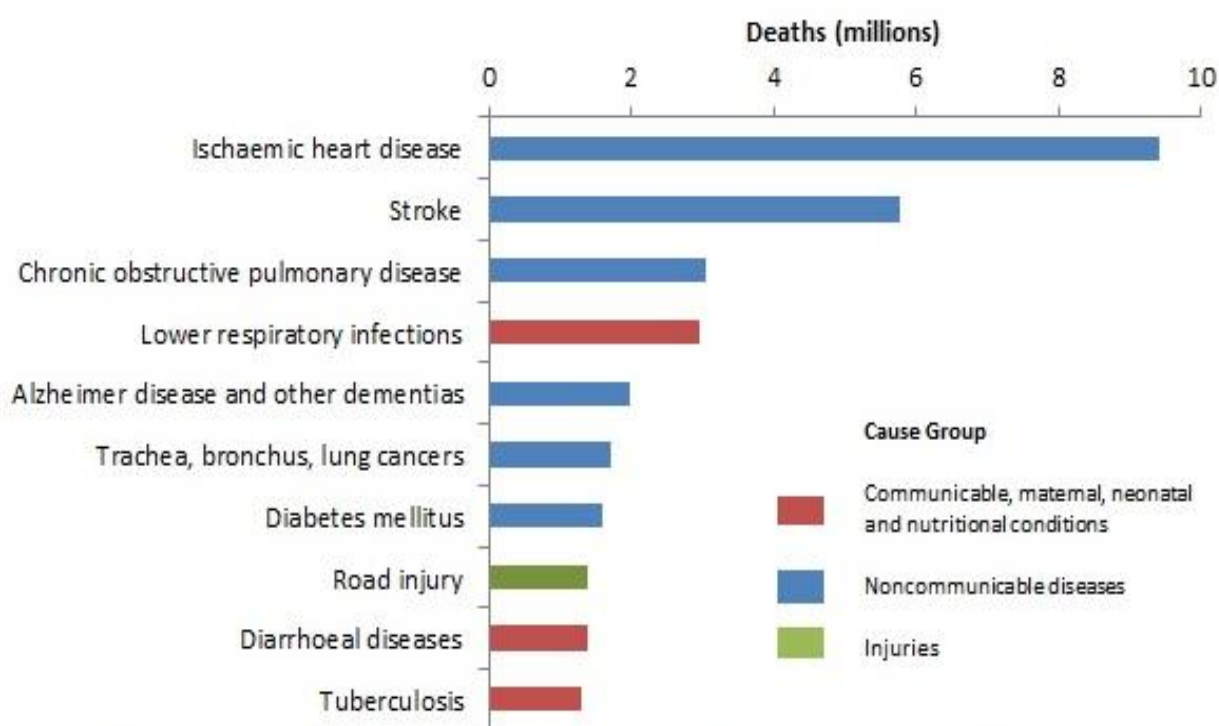
Measuring how many people die each year and why they died is one of the most important means – along with gauging how diseases and injuries are affecting people – for assessing the effectiveness of a country’s health system.

Cause-of-death statistics help health authorities determine the focus of their public health actions. A country in which deaths from HD and diabetes rise rapidly over a period of a few years, for example, has a strong interest in starting a vigorous programme to encourage lifestyles to help prevent these illnesses. Similarly, if a country recognizes that many children

are dying of pneumonia, but only a small portion of the budget is dedicated to providing effective treatment, it can increase spending in this area.

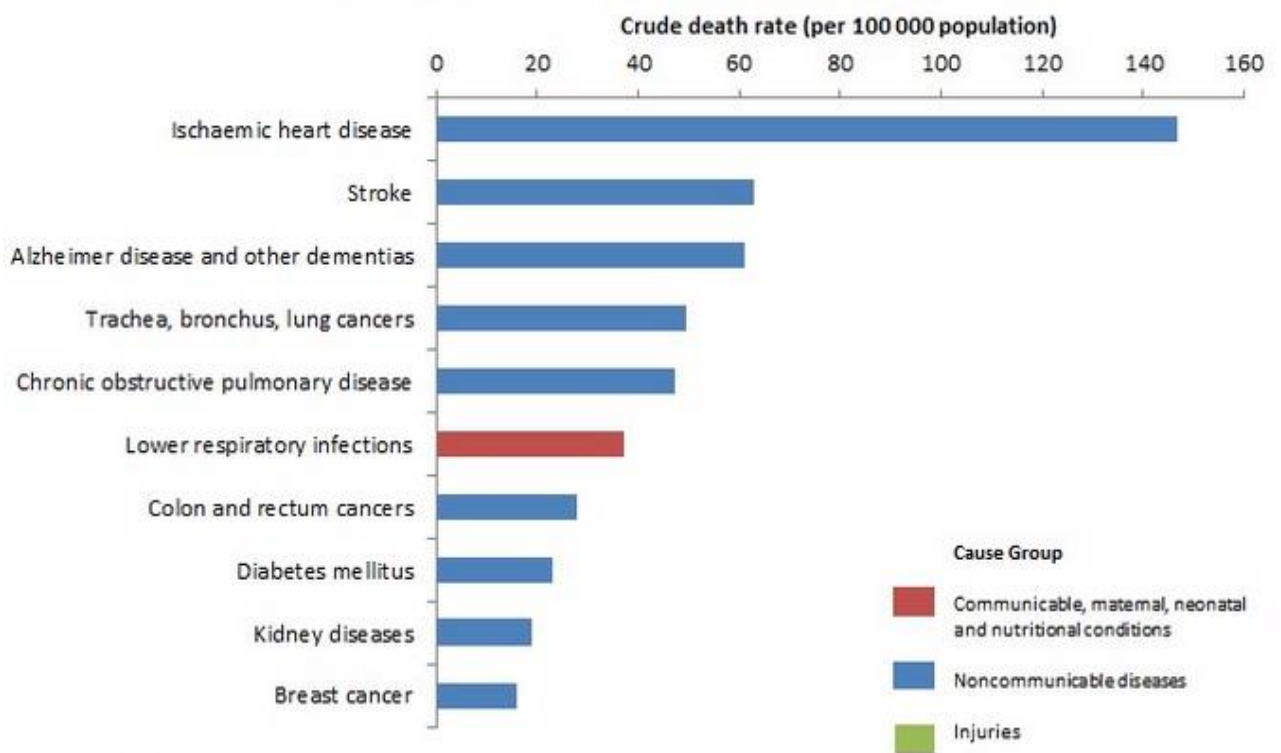
HIC have systems in place for collecting information on causes of death. Many LIMC do not have such systems, and the numbers of deaths from specific causes have to be estimated from incomplete data. Improvements in producing high quality cause-of-death data are crucial for improving health and reducing preventable deaths in these countries.

Stroke is the second most frequent cause of death worldwide ranked after ischemic heart disease (Donnan et al., 2008; Lozano et al., 2012; Murray et al., 1997; WHO, 2014) (**Figures 13-17**), accounting for 6.7 million deaths in 2012 (approximately 12% of the total) (WHO, 2014).



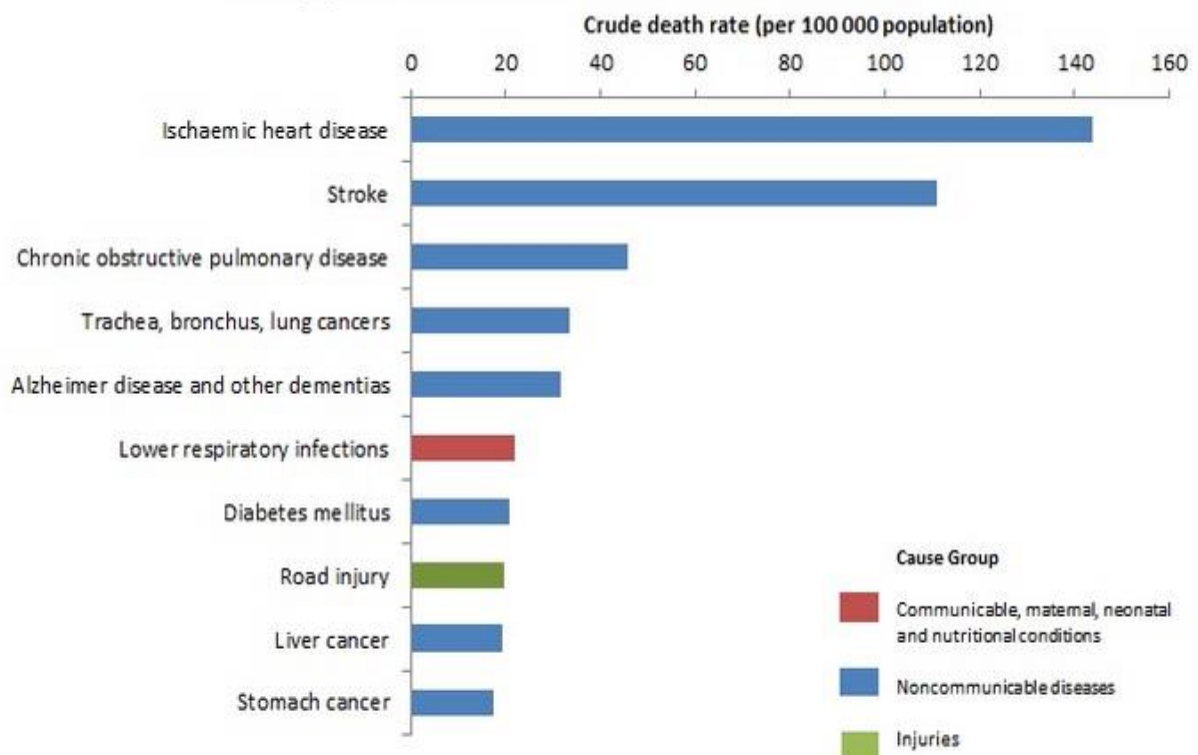
Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

Figure 13 Top 10 global causes of deaths, 2016 (WHO 2018)



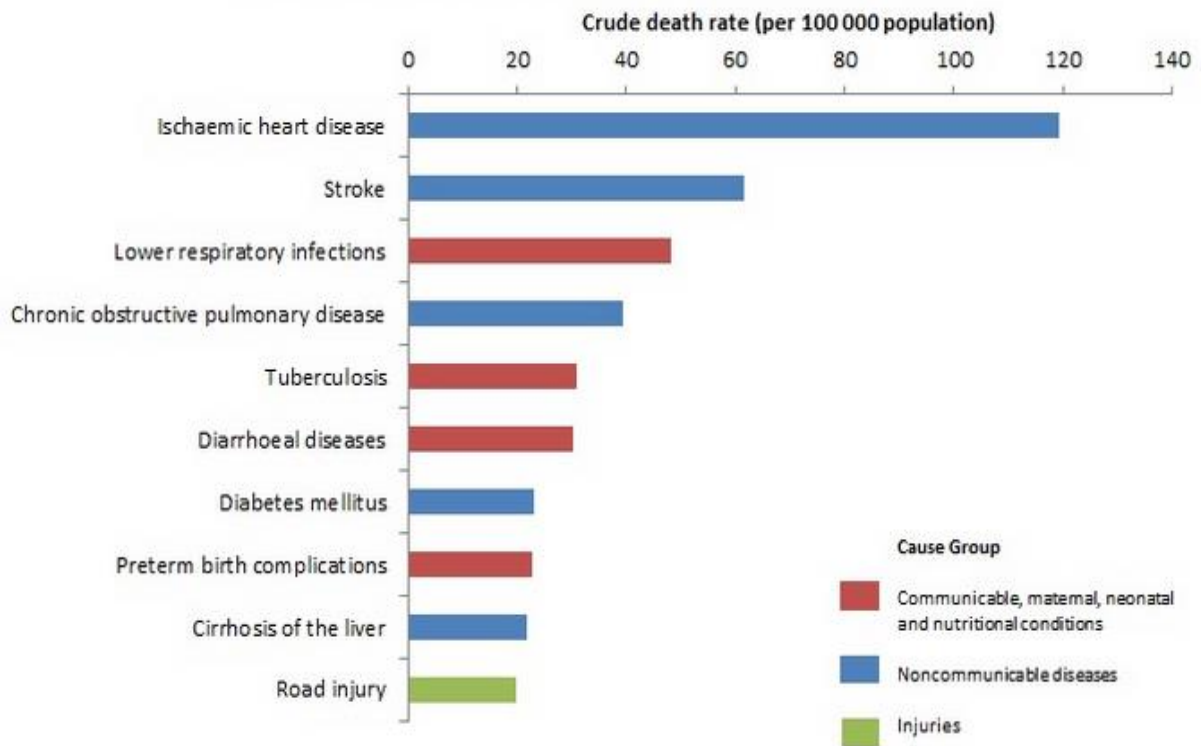
Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018. World Bank list of economies (June 2017). Washington, DC: The World Bank Group; 2017 (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906319-world-bank-country-and-lending-groups>).

Figure 14 Top 10 causes of deaths in high-income countries, 2016 (WHO 2018)



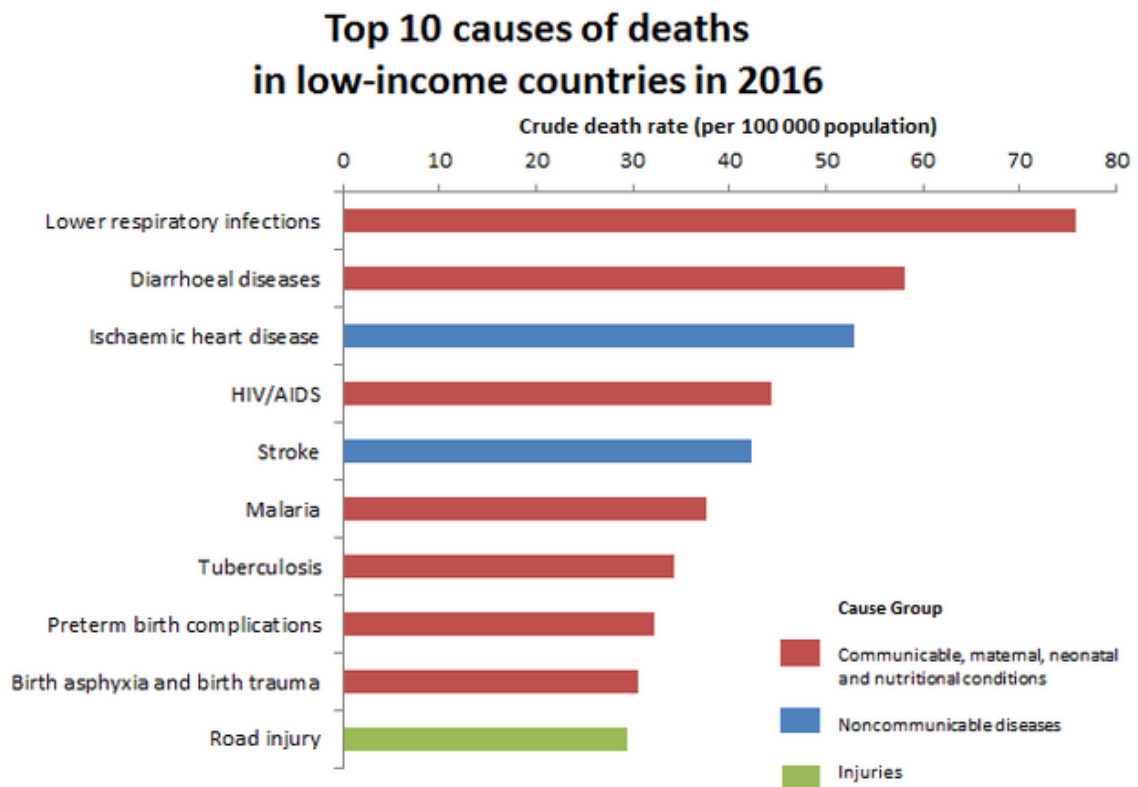
Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018. World Bank list of economies (June 2017). Washington, DC: The World Bank Group; 2017 (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906319-world-bank-country-and-lending-groups>).

Figure 15 Top 10 causes of deaths in upper-middle-income countries, 2016 (WHO 2018)



Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018. World Bank list of economies (June 2017). Washington, DC: The World Bank Group; 2017 (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906319-world-bank-country-and-lending-groups>).

Figure 16 Top 10 causes of deaths in lower-middle-income countries, 2016 (WHO 2018)



Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018. World Bank list of economies (June 2017). Washington, DC: The World Bank Group; 2017 (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906319-world-bank-country-and-lending-groups>).

Figure 17 Top 10 causes of deaths in low-income countries, 2016 (WHO 2018)

There are substantial geographic disparities in stroke mortality (**Figure 18**), with higher rates in the southeastern US, known as the “stroke belt”. These geographic differences have existed since at least 1940 (Lanska, 1993), and despite some minor shifts (Casper et al., 1995), they persist (Casper et al., 2008; Perry and Roccella, 1998). Within the stroke belt, a “buckle” region along the coastal plain of North Carolina, South Carolina, and Georgia has been identified with an even higher stroke mortality rate than the remainder of the stroke belt. Historically, the overall average stroke mortality has been $\approx 30\%$ higher in the stroke belt than in the rest of the nation and $\approx 40\%$ higher in the stroke buckle (Howard et al., 1997).

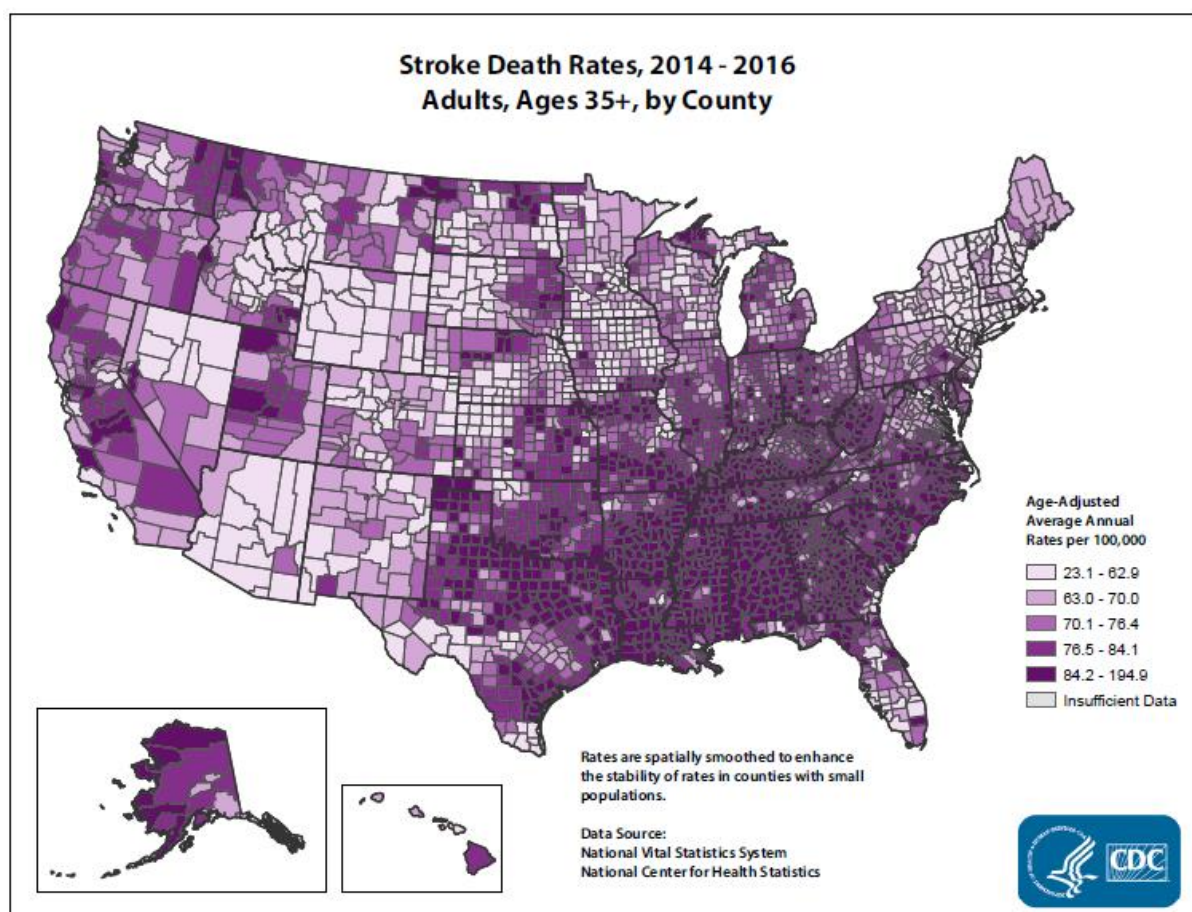


Figure 18 Stroke death rates, Total Population 35+, 2014 through 2016

- Every 5-6 seconds someone, somewhere, regardless of age or gender will die from stroke (Stroke Foundation; WHO, 2014). Almost 1 in 8 deaths worldwide are caused by stroke (WHO, 2014).
- About 10-15% of people with SAH die before reaching hospital (Intercollegiate Stroke Working Party, 2016).

- Eight to twelve percent of IS and 37% to 38% of haemorrhagic strokes result in death within 30 days (Roger et al., 2012; Woo et al., 1999).
- In 2013 (GBD 2013 Mortality and Causes of Death Collaborators, 2015):
 - Stroke deaths accounted for 11.8% of total deaths worldwide. There were 6.5 million stroke deaths worldwide, making stroke the second-leading global cause of death behind IHD. A total of 3.3 million individuals died of IS and 3.2 million of hemorrhagic stroke.
 - The absolute number of stroke deaths increased 40.2% between 1990 and 2013; however, the age-standardized death rate decreased 22.5%. Age-standardized death rates decreased 19.6% and 25.9% for ischemic and hemorrhagic stroke, respectively, since 1990.
- In 2010, the mean age of stroke-related death in HIC was 80.4 years compared with 72.1 years in LIMC (Lozano et al., 2012). Between 1990 and 2010, IS mortality decreased 37% in HIC and 14% in LIMC. Hemorrhagic stroke mortality decreased 38% in HIC and 23% in LIMC (Krishnamurthi et al., 2013).
- Europe averages approximately 650,000 stroke deaths each year (The internet stroke center). In 2008, there were approximately 1.3 million deaths from stroke in Europe, accounting for almost 14% of all deaths (WHO, 2008).
- In 2000, stroke accounted for 7% of all deaths – 15,409 Canadians (The internet stroke center).
- In the US in 2014 (NCHS, 2014):
 - Stroke accounted for ≈1 of every 20 deaths, on average, every 4 minutes someone died of a stroke. The number of deaths with stroke as an underlying cause was 133 103.
 - Approximately 60% of stroke deaths occurred outside of an acute care hospital.
 - Non-Hispanic black men and women had higher age-adjusted death rates for stroke than non-Hispanic white, non-Hispanic Asian, non-Hispanic Indian or Alaska Native, and Hispanic men and women in the US.
 - Women accounted for 58% of US stroke deaths. More women than men die of stroke each year because of a larger number of elderly women than men.
 - From 2004 to 2014, the age-adjusted stroke death rate decreased 28.7% (from 51.2 per 100 000 to 36.5 per 100 000), and the actual number of stroke deaths declined 11.3% (from 150 074 deaths to 133 103 deaths).

The proportion of deaths due to stroke rose from 9.7% to 11.8% between 1990 and 2013 (Figure 19). The increase in the contribution of deaths was largely attributable to LIMC (Feigin et al., 2015); there was no significant rise in the proportion of deaths due to stroke in HIC (Krishnamurthi et al., 2015).

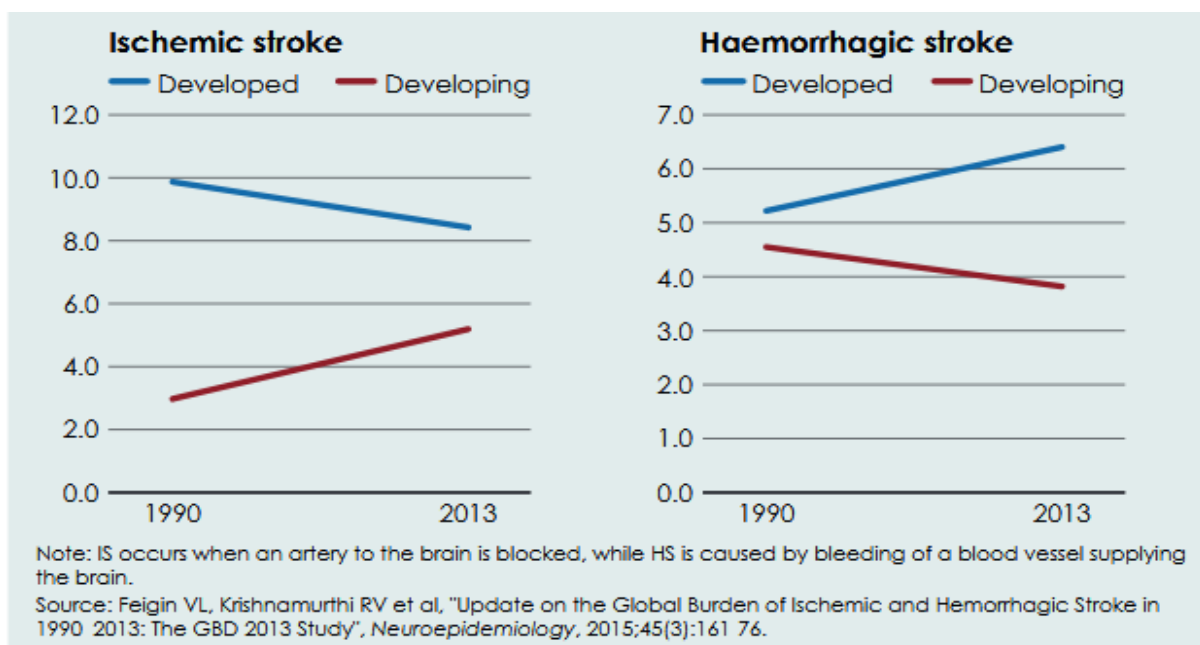
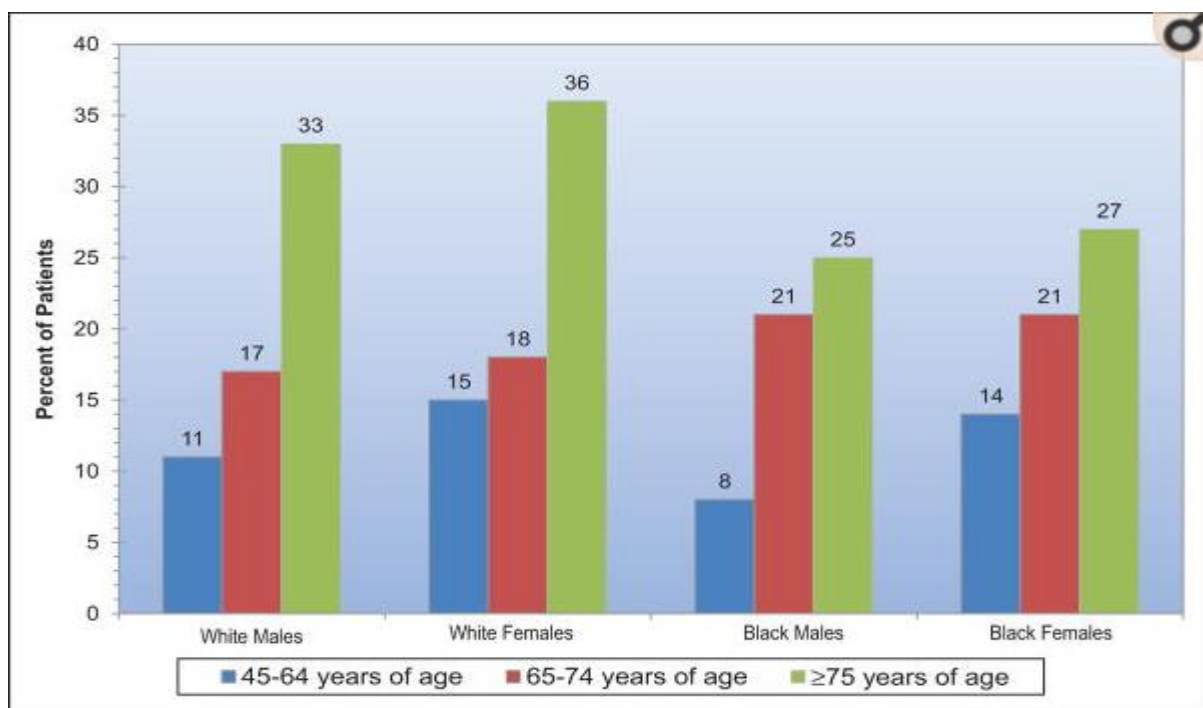
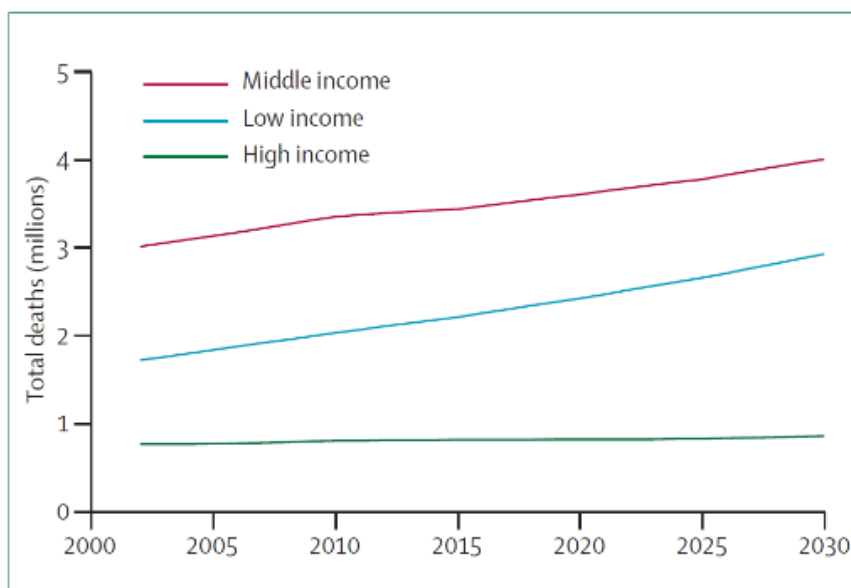


Figure 19 Trends in contribution to death due to ischemic and hemorrhagic stroke as a percentage of all conditions between developed and developing countries



Source: Pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the National Heart, Lung, and Blood Institute.

Figure 20 Probability of death within 1-year after first stroke



Source: Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol*, 2007, 6:182-187.¹¹

Figure 21 Projected trends for stroke deaths by World Bank income group 2002-30

1.8.4. Disability-adjusted life years

The measures of ill-health used so far (incidence, prevalence and mortality or years of life lost) do not give a complete picture of the burden of disease borne by individuals in different communities. DALY is the summary measure used to give an indication of overall burden of disease. One DALY represents the loss of the equivalent of one year of full health. Using DALYs, the burden of diseases that cause premature death but little disability (such as drowning or measles) can be compared to that of diseases that do not cause death but do cause disability (such as cataract causing blindness).

DALYs for a year combine the following:

- Years of life lost for years of life lost due to deaths in this year
- Years lost due to disability for equivalent healthy years of life lost through living in states of less than full health for cases of disease and injury incident in this year.

Stroke is a major cause of disability worldwide (Donnan et al., 2008). According to the World Heart Federation, stroke is the second leading cause of disability ranked after dementia (WHF, 2017). Surviving stroke can be considered to be worse than death, with stroke victims facing

an uncertain future and a life that may be severely affected by disability such as loss of vision and/or speech, paralysis and confusion (WHF, 2017)

According to the World Heart Federation, every year 15 million people worldwide have a stroke; of these, almost 6 million die and another 5 million are left with permanent disabilities (WHF, 2017). Stroke was the third leading cause of DALYs lost worldwide in 2012, according to WHO data. In all, 113 million DALYs were lost as a result of stroke in 2013 (Feigin et al., 2015). The contribution of DALYs due to stroke as a share of all conditions rose from 3.5% to 4.6% between 1990 and 2013 (**Figure 22**). The increase in the contribution of DALYs was largely attributable to LIMC (Feigin et al., 2015); there was no significant rise in the proportion of DALYs due to stroke in HIC (Krishnamurthi et al., 2015).

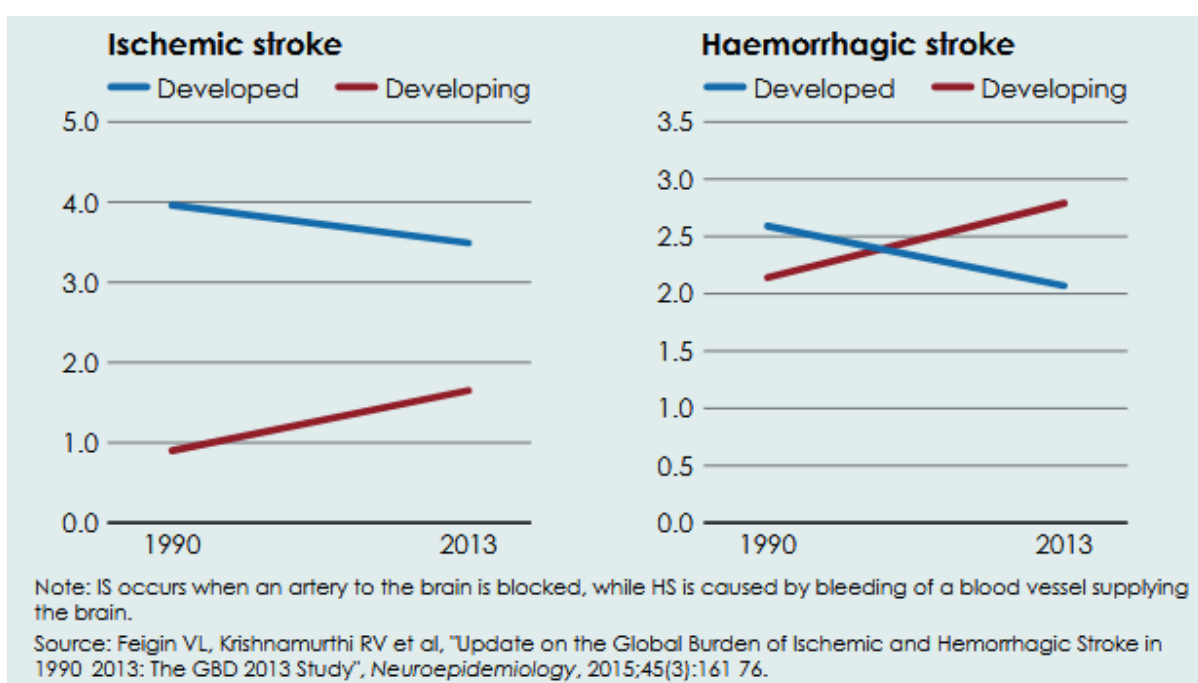


Figure 22 Trends in contribution to DALYs due to ischemic and hemorrhagic stroke as a percentage of all conditions between developed and developing countries

Stroke was among the top 18 diseases contributing to years lived with disability in 2010; of these 18 causes, only the age-standardized rates for stroke increased significantly between 1990 and 2010 ($P < 0.05$) (US Burden of Disease Collaborators, 2013). In 2010, 39.4 million DALYs were lost because of IS and 62.8 million because of hemorrhagic stroke (64% and 85%, respectively, in LIMC) (Krishnamurthi et al., 2013). The number of lost DALYs ranged from 398 (Australia) to 5227 (Afghanistan) per 100,000 in 2010 (Feigin et al., 2014). Around 78% of lost DALYs are found in LIMC (Feigin et al., 2014).

1.8.5. Quality Of Life post-stroke

The assessment of quality of life (QOL) after stroke is becoming common with the recognition that evaluation of treatment should include quality as well as quantity of survival (Buck et al., 2000). The results of treatment are appraised by applying tests that evaluate physical limitations and/or functional impairments (Hourihane et al., 1999; van der Lee et al., 1999). These tests, however, do not give us a measure of the patient's own perception of the mental and emotional effects of the bodily disabilities. Because of this, there has been a growing interest in tests that measure the health related QOL of poststroke patients. This is used in addition to the scales of physical impairments (Krančiukaitė and Rastenytė, 2006). The combined scales are an indication of therapeutic effectiveness (Williams, 1998). Measuring QOL mostly comprises functional, physical, cognitive, psychological, and social elements. The results of these measures fairly accurately represent the patient's own perception of his/ her functioning and general health. Taking into consideration the way in which patients view their own health situation is the most important element of patient-centered health care (Krančiukaitė and Rastenytė, 2006). Recording self-reported QOL must be integrated element of poststroke evaluation and treatment (Saladin, 2000).

1.8.5.1 Quality of life measures

QOL instruments can be divided into generic and disease-specific scales:

1.8.5.1.1 Generic descriptions of quality of life measures

Generic scales address general health concepts not specific to any age, disease, or treatment (Furmonavičius, 2004). The four most stroke-relevant generic measures are:

Medical Outcomes Short Form Health Survey (SF-36)

This is an often-used measurement scale which was suggested by the Agency for Health Care Policy and Research in the Poststroke Rehabilitation Clinical Practice Guidelines (AHCPR, 1996). This instrument is a 36-item questionnaire completed by the patient him/herself. The items are grouped into eight domains which embrace a large range of physical activities and psychosocial cognition also including the evaluation of general health status (**Appendix 3**). The scores on a scale ranges from 0 to 100; a higher score indicates better health.

Medical Outcomes Short Form Health Survey (SF-12)

The SF-12 is an abbreviated version of the SF-36. The SF-12 generates the physical and mental component summary (PCS and MCS, respectively) scores of the SF-36 with considerable accuracy, while imposing minimal burden on respondents (Ware et al., 1996). It was demonstrated that PCS and MCS scores of the SF-36 were replicable by the SF-12 (Pickard et al., 1999).

Sickness Impact Profile (SIP)

The SIP is a generic measure designed to subjectively evaluate the impact of illness/disease on physical and psychosocial functioning. The test consists of two domains (physical and psychosocial), twelve categories and 136 items. Physical categories include: ambulation, mobility, body care/movement. Psychosocial categories include: social interaction, communication, alertness behavior, emotional behavior, sleep and rest, eating, home management, recreation and pastimes, and employment. Questions are phrased in the present tense, and ask about how the patient is feeling at the time of test administration. Question responses are binary (“Yes/No”) and patients are asked to check items that apply to them (American Thoracic Society, 2007). The test was designed to measure the effectiveness or outcomes of health care (Bergner et al., 1981). Scores can be obtained for individual domains and categories, as well as an overall score. Items are weighted based on a standardized weighting method. The overall score is given as a percentage; a higher score indicates a poorer level of health.

Euroqol

Euroqol is a measurement scale which has been developed by the Euroqol group. It was created as a standardized generic scale used for the evaluation of patient health status and has been used for this objective in varying clinical populations. The Euroqol questionnaire consists of only six items and covers six domains (mood, mobility, daily practice, pain and discomfort, family and leisure activities and self-maintenance). The score for each item ranges from 1 to 3, whereby 1 signifies “no problems” and 3 represents “extreme problems”. In addition to this scale, the Euroqol uses a visual analogue scale from 0 to 100 to furnish a general estimate of health-related QOL, where 0 signifies “worst imaginable health” and 100 “best imaginable health” (Buck et al., 2000).

1.8.5.1.2 Stroke-specific quality of life measures

Although stroke is a major problem, the best method for measuring the outcome of stroke is not clear, partly due to the heterogeneity of stroke signs and symptoms (Williams, 1998).

Three disease-specific QOL measures were developed for the use in stroke survivors:

The Stroke Specific Quality of Life Measure (SSQOL)

This instrument is a tool for poststroke-specific QOL scales (Williams et al., 1999). Interviews with stroke patients formed the basis for 49-item and 12-domain questionnaire (**Appendix 4**). Patients must respond to each question of the SS-QOL with reference to the past week. Items are rated on a 5-point Likert scale. Higher scores indicate better functioning. The SS-QOL yields both domain scores and an overall SS-QOL summary score. The domain scores are unweighted averages of the associated items while the summary score is an unweighted average of all twelve domain scores.

The Stroke Adapted Sickness Impact Profile (SASIP30)

The SASIP30 was developed from the original 136-item Sickness Impact Profile (SIP-136), and assesses quality of life in patients who have sustained a stroke. The scale was developed specifically for use in stroke outcome research in order to overcome the major problem observed with the SIP-136, its length (van Straten et al., 1997).

The Stroke Impact Scale (SIS)

The Stroke Impact Scale (SIS) is a stroke-specific, self-report, health status measure. It was designed to assess multidimensional stroke outcomes, including strength, hand function Activities of Daily Living / Instrumental Activities of Daily Living (ADL/IADL), mobility, communication, emotion, memory and thinking, and participation. The SIS can be used both in clinical and in research settings. The SIS version 3.0 includes 59 items and assesses 8 domains. Each item is rated using a 5-point Likert scale (1 = an inability to complete the item; 5 = no difficulty experienced at all). An extra question on stroke recovery asks that the client rate on a scale from 0–100 how much the client feels that he/she has recovered from his/her stroke (0 = no recovery; 100 = full recovery).

1.8.5.2 Quality of life determinants

Several studies have shown that by far the largest part of the patients experience and report a decline in QOL after stroke (Nydevik and Hulter-Asberg, 1992; Williams et al., 1999), and this even applies to persons who have suffered only a minor stroke (Williams et al., 1999). There are a number of factors which seem to be contributing towards a decline in QOL of stroke patients: social support, laughter and negative feelings frequencies (Owolabi, 2008), NIHSS, Barthel Index (Lopez-Espuela, 2015), advanced age (Hackett et al., 2000; Nydevik and Hulter-Asberg, 1992), function status measured by modified Rankin Scale and depression were independent determinants of poor health related QOL (Abubakar and Isezuo, 2012). Failure to maintain or re-establish social ties, except for those with family members, seems to be an important determinant of poor QOL in long-term survivors of stroke (Aström et al., 1992), whereas high levels of social support have been shown to be related to a better outcome (Wyller et al., 1998). The effect of the after-stroke time factor on QOL is still contentious. A decline in the QOL over a 6- to 24-month period after the stroke event has been documented (Nydevik and Hulter-Asberg, 1992).

1.8.5.3 Caregivers quality of life

Stroke has a great impact not only on the patients' lives but also on the lives of their caregivers. The carers of stroke patients provide informal care ranging from physical help to psychosocial support. As a result, these carers may experience high levels of burden, associated with characteristics of the patients and of the carers themselves. This burden can result in a deterioration of the carers' health status, social life and well-being. About 80% of stroke patients return home after the acute hospitalization and at least one-half of them require permanent or temporary help from other people in the home setting. This help is usually provided by the closest family member often a spouse or a child, most frequently a daughter who lives with the patient. Family caregivers provide basic personal care, help the patients to perform daily activities, give emotional support, and organize medical and social community service (Vincent et al., 2009). Around 42% of stroke patients report a negative change in their relationship with their partner after a stroke (McKevitt et al., 2011).

1.8.5.4 Depression post-stroke

Around a third of stroke survivors experience depression after their stroke (Ayerbe et al., 2015; Hackett et al., 2005). Several meta-analyses have revealed that approximately 1 of every 3 stroke survivors develops post-stroke depression (Benjamin et al., 2017). The most recent meta-

analysis involving 61 studies (n=25 488) revealed similar results, with depression being present in 33% (95% CI, 26%–39%) of patients at 1 year after stroke, with a decline beyond 1 year: 25% (95% CI, 16%–33%) up to 5 years and 23% (95% CI, 14%–31%) at 5 years (Hackett et al. 2014).

Post-stroke depression is associated with higher mortality. A meta-analysis of 13 studies involving 59 598 people revealed a pooled OR for mortality at follow-up of 1.22 (95% CI, 1.02–1.47) (Bartoli et al., 2013).

Twelve RCTs (n=1121) suggested that antidepressant medications could be effective in treating post-stroke depression, with a beneficial effect of antidepressants on remission (pooled OR for meeting criteria for depression, 0.47; 95% CI, 0.22–0.98) and response, measured as a >50% reduction in mood scores (pooled OR, 0.22; 95% CI, 0.09–0.52) (Hackett et al. 2008).

Six trials (n=675) suggested that brief psychosocial interventions could be useful and effective in treatment of post-stroke depression (Alexopoulos et al. 2012; Hackett et al. 2008).

A meta-analysis of 8 RCTs assessing the efficacy of preventive pharmacological interventions among 776 initially non-depressed stroke patients revealed that the likelihood of developing post-stroke depression was reduced among subjects receiving active pharmacological treatment (OR, 0.34; 95% CI, 0.22–0.53), especially after a 1-year treatment (OR, 0.31; 95% CI, 0.18–0.56), and with the use of a selective serotonin reuptake inhibitor (OR, 0.37; 95% CI, 0.22–0.61). All studies excluded those with aphasia or significant cognitive impairment, which limits the generalizability (Salter et al., 2013).

1.8.6. Stroke clinical outcome and measures

1.8.6.1 The modified Rankin Scale

The modified Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It has become the most widely used clinical outcome measure for stroke clinical trials (Saver et al., 2010; Wilson et al., 2002). The scale runs from 0-6, running from perfect health without symptoms to death (**Fig. 23**)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

Figure 23 *The modified Rankin Scale*

1.8.6.2 The Barthel scale

The Barthel scale or Barthel activities of daily living (ADL) index is an ordinal scale used to measure performance in activities of daily living. Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses ten variables describing activities of daily living and mobility. The scale runs from 0–100 (**Figures 24,25**). A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital.

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24–48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

Figure 24 *The Barthel ADL Index guidelines*

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Figure 25 The Barthel ADL Index

1.8.6.3 Stroke clinical outcomes

Stroke causes a greater range of disabilities than any other condition (Adamson et al., 2004):

- It is estimated that 60% of stroke survivors have visual problems immediately after their stroke and this reduces to about 20% by three months after stroke (Rowe, 2013).

- Around a third of stroke survivors experience some level of aphasia (Berthier, 2005; Dickey et al., 2010; Engelter et al., 2006).
- Over three quarters of stroke survivors report arm weakness (Lawrence et al., 2001), which can make it difficult for people to carry out daily living activities.
- Almost three quarters of stroke survivors report leg weakness (Lawrence et al., 2001), which can cause difficulty walking and balancing. Over half of people who have a stroke need help from another person to be able to walk (ISD Scotland, 2016).
- Loss of bladder and bowel control is a common problem for stroke survivors. Around half of stroke survivors experience problems with bladder control (Lawrence et al., 2001).
- Around half of stroke survivors have problems swallowing (Lawrence et al., 2001). This can make eating and drinking difficult, and delays in hospital assessments for swallowing are associated with a higher risk of pneumonia (Bray et al., 2017).
- Four out of 10 stroke survivors leave hospital requiring help with daily living activities but almost a third receive no social service visits (Royal College of Physicians SSNAP, 2016).
- Stroke is also a leading cause of dementia (Owolabi et al., 2015).

Stroke is a leading cause of serious long-term disability in the US. Approximately 3% of men and 2% of women reported that they were disabled because of stroke (CDC, 2009). After stroke, women often have greater disability than men. For example, an analysis of community-living adults (>65 years of age) found that women were half as likely to be independent in activities of daily living after stroke, even after controlling for age, race, education, and marital status (Whitson et al., 2010). A meta-analysis of >25 studies examining sex differences in long-term outcomes among stroke survivors found that women tended to have worse functional recovery and hence greater long-term disability and handicap (Gall et al., 2012).

1.8.7. Cost of Stroke

Stroke is a costly disease from human, family and societal perspectives. Starting from human costs, stroke is the second leading cause of death worldwide, accounting for 10% of total deaths (Lopez et al., 2006), and a leading cause of disability (Donnan et al., 2008). Annually, about 16 million first-ever strokes occur in the world, causing a total of 5.7 million deaths (Strong et al., 2007). Stroke is one of the principal causes of hospital and care-home resource utilization (Wolfe, 2006). Despite its enormous impact on countries' socio-economic development, this

growing crisis has received very little attention to date (Walter et al., 2017) and stroke research remains severely underfunded. There is therefore much research interest in quantifying the costs of stroke.

A costing study consists of the measurement and valuation of resources related to an illness, under which resources consumed are measured and ascribed using a monetary value (Leal et al., 2006). One of the main types of costing study takes into account the costs incurred by patients from disease onset to end of follow-up or death, and is generally used to estimate the cost of a particular disease or event per patient (Payne et al., 2002).

Cost of illness analysis is the main method of providing an overall view on the economic impact of a disease (Tarricone, 2006). Such studies have been used to set priorities for health care policies and describe resource allocations for various diseases. Results of costing studies are useful to inform decisions about service provision and resource allocation, and to estimate the cost-effectiveness of specific interventions to prevent or treat illness (Drummond et al., 2005). Reliable estimates of the costs of disease are also valuable to other researchers, particularly as an input to decision-analytic models, which are becoming ever more popular to assess the cost-effectiveness of health care interventions. These allow synthesis of available evidence, including cost data, allow extrapolation of trial results, and are useful to determine cost-effectiveness when RCTs are either too costly or inappropriate (Sculpher et al., 2006). Cost estimates can be derived from expert opinion or, as in most cases, from published research based on patient-level data (ie, observational studies or RCTs).

Stroke costs the US an estimated US\$ 34 billion each year. This total includes the cost of health care services, medicines to treat stroke, and missed days of work (Benjamin et al., 2017). In the US, the total cost of stroke in 2010 was estimated at US\$ 73.7 billion by the US National Stroke Association; this includes the direct cost of medications to treat stroke as well as healthcare services, for example in hospitals or nursing homes, by physicians, home healthcare etc (making up more than 60% of the total costs) and indirect costs such as lost productivity (making up almost 40% of the total costs) (National Stroke Association, 2015).

In Brazil, the mean total costs of initial hospitalization were US\$4,101±4,254 for ICH and US\$1,902±1,426 for IS. Aggregate national health care expenditures for acute treatment of incident ICH were US\$ 122.4 million (range 30.8-274.2) and US\$ 326.9 million for IS (range 82.4-732.2) (Christensen et al., 2009).

In Argentina, the mean total costs of initial hospitalization were US\$12,285±14,336 for ICH and US\$3888±4018 for IS. Aggregate national healthcare expenditures for acute treatment of incident ICH were US\$194.2 million (range 97.1-388.4) and US\$239.9 million for IS (range 119.9-479.7) (Christensen et al., 2009).

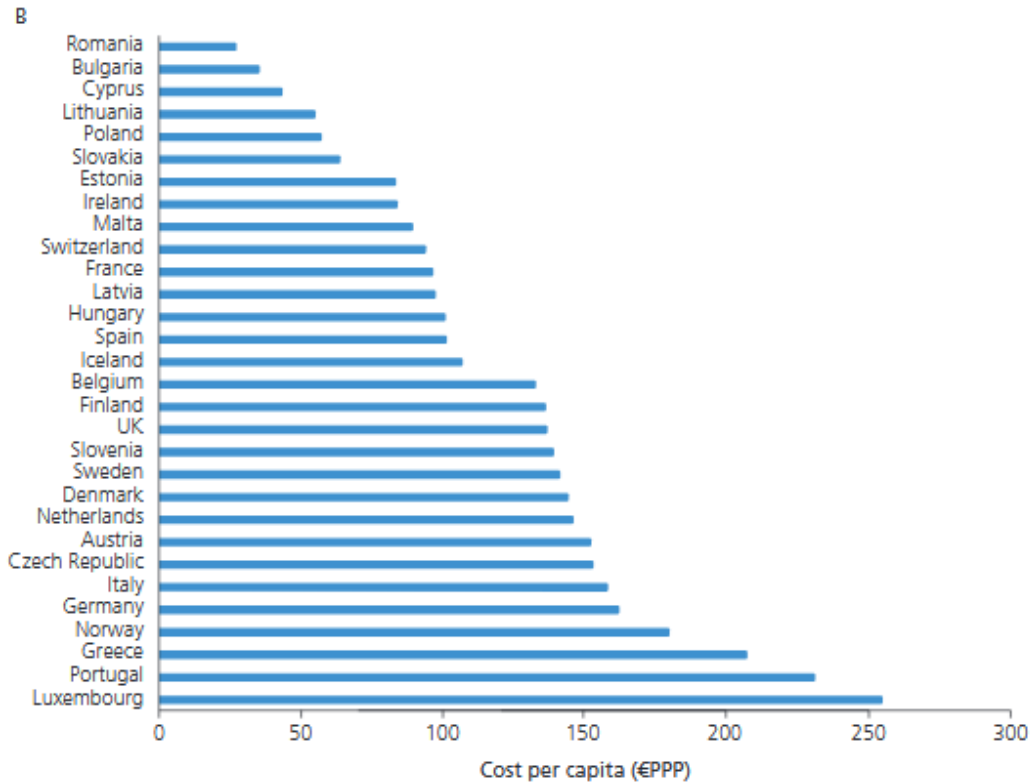
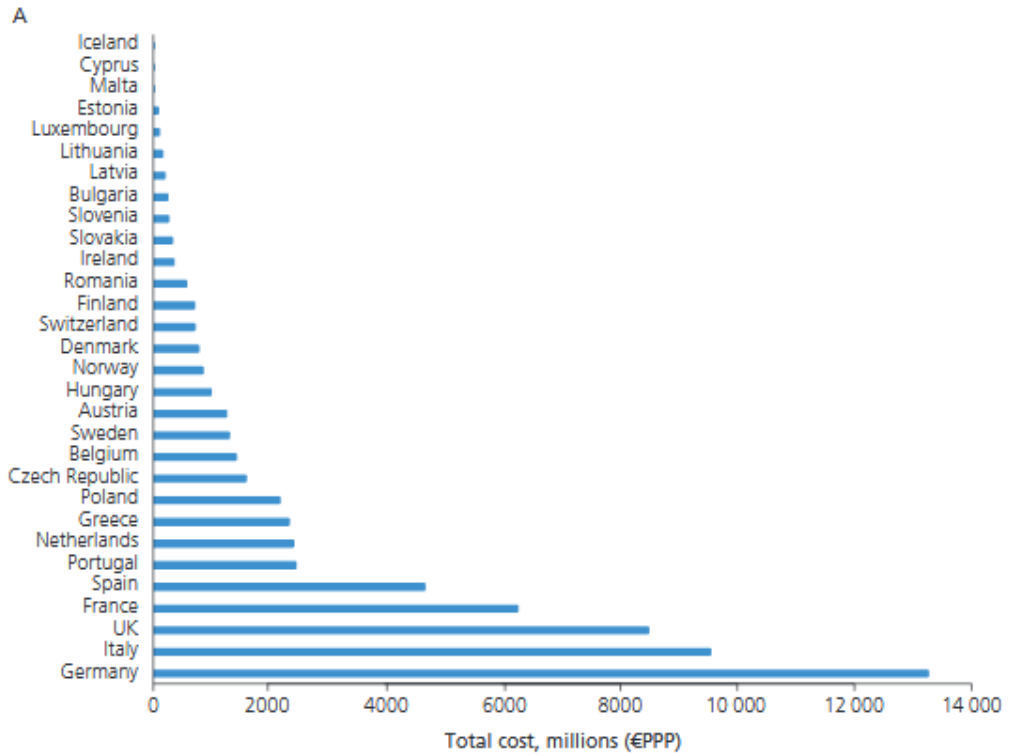
In the United Kingdom, a research published in 2009 attempted to estimate the annual cost of stroke to the United Kingdom economy (Saka et al., 2009). The research included diagnosis, inpatient care and outpatient care in its estimate of direct costs; its estimate of indirect costs included income loss and social benefit payments to stroke survivors. In all, the research put the total cost of the treatment of stroke and the productivity loss arising from stroke at £ 8.9 billion (US\$ 12.9 billion) annually, with direct care accounting for around half of this amount, informal care costs for 27% and indirect costs for 24%.

In Italy, one-year healthcare and societal costs amounted to €11,747 and €19,953 per stroke survivor, respectively. The major cost component of societal costs was informal care accounting for €6,656 (33.4% of total), followed by the initial hospitalisation, (€5,573; 27.9% of total), rehabilitation during follow up (€4,112; 20.6%), readmissions (€439) and specialist and general practitioner visits (€326). Mean drug costs per patient over the follow-up period was about €50 per month. Costs associated to the provision of paid and informal care followed different pattern and were persistent over time (ranging from €639 to €597 per month in the first and the second part of the year, respectively) (Fattore et al., 2012).

In Greece, the direct in-hospital cost for all stroke cases was €1,551,445 for a total of 4674 days (€332 per day in-hospital). The mean in-hospital cost per stroke patient was €3625 ±2695. Hemorrhagic strokes were significantly more expensive than the ischemic strokes (mean €5305±4205 and €3214±1976, respectively) and lacunar strokes the least expensive among ischemic stroke subtypes (Gioldasis et al., 2008).

In the European Union 27 countries, the annual economic cost of stroke was an estimated €27 billion: €18.5 billion (68.5%) for direct costs and €8.5 billion (31.5%) for indirect costs. An additional €11.1 billion was calculated for the value of informal care (British Geriatrics Society, 2009). In another European Union study, the financial burden of stroke was about €62 billion (US\$70 billion) per year and accounted for around for 2-3% of the entire healthcare expenditure in the region (StopAfib organisation, 2012).

In Europe, the cost of stroke was €64.1 billion €PPP 2010 (Gustavsson et al, 2011) (**Figure 26**)



A: Total costs; B: cost per capita. Data taken from Gustavsson *et al.* (2011).
 Direct healthcare cost is estimated to be 66% of the total cost of stroke.
 PPP, purchasing power parity; UK, United Kingdom.

Figure 26 Costs attributable to stroke in Europe in 2010.

In Turkey, the average cost of stroke was US\$1677 ± 2964 (29.9% medicine, 19.9% laboratory, 12.8% neuroimaging, and 38% beds and staff) (Asil *et al.*, 2011).

In Pakistan, the average total cost was 70,714 rupees (US\$1179) which included average radiology cost; 12,507 rupees (US\$208), average laboratory cost; 8365 rupees (US\$139), average pharmacy cost; 13,320 rupees (US\$222) and average bed/room charges; 27,552 rupees (US\$459) (Khealani et al., 2003).

Strokes mainly affect individuals at the peak of their productive life (Walter et al., 2016). People of working age who have had a stroke are 2 to 3 times more likely to be unemployed 8 years after their stroke (Maaijwee et al., 2011). Around 1 in 6 stroke survivors experience a loss of income after stroke (McKevitt et al., 2011).

2. Situation in Lebanon

Lebanon is an Arab country of the Middle East region classified among upper-middle income country of the Eastern Mediterranean Region (WHO, 2015). Available studies on non communicable diseases have shown alarmingly high prevalence of cardiovascular risk factors such as hypertension 36% (Matar et al., 2015), diabetes 14% (Tohme et al., 2005), obesity 26% (Chamieh et al., 2015), and behavioral risk factors such as smoking (cigarettes 38.5% and waterpipe 22.4%) (Sibai and Hwalla, 2008) and insufficient physical activity (38%) (WHO, 2015) among Lebanese adults. However, studies focusing on stroke in Lebanon are limited.

The incidence rate of stroke in Lebanon has remained unstudied so far. The studies presenting the overall stroke prevalence rate are scarce and show a prevalence varying between 0.5% and 3.9% (Farah et al., 2015; Jurus et al., 2009; Lahoud et al., 2016).

A risk of stroke score (ROSS) was developed for screening individuals at risk of stroke in the Lebanese population. A hospital-based case-control study was conducted for the score generation. A score <2 points indicated a 94.4% high negative predictive value of stroke. A score >10 points had more than 85.4% positive predictive value of stroke (El-Hajj et al., 2018a).

A diagnosis score for stroke (DS-stroke) at emergency among the Lebanese population by using stroke risk factors and symptoms was developed in order to diagnose stroke patients at emergency department. A hospital-based case-control study was conducted for the score generation. A score <4 points indicated a high negative predictive value of stroke of 97.3%. A score ≥ 4 points indicated a positive predictive value of stroke of 91.3% (El-Hajj et al., 2018b).

A national epidemiological study assessed the association between self-reported indoor and outdoor pollution and stroke and mini-stroke in Lebanon (Salameh et al., 2018).

A retrospective study evaluate the existence of genetic mutation (MTHFR and Factor V gene mutations) in different types of cerebral strokes in previously healthy young adults (Araji et al., 2014).

A retrospective study analyzed the prevalence of all hemorrhagic stroke and ischemic stroke subtypes in a Lebanese hospital-based inpatient population. Ischemic stroke subtypes were further categorized according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (Adams et al., 1993) and their correlations with validated stroke risk factors and with socio-demographic characteristics of the sample were evaluated (Lahoud et al., 2017).

Moreover, stroke is the second leading cause of death in Lebanon after ischemic heart disease, killing 2000 people in 2012 (9.4% of total death) (WHO, 2015). It is furthermore a major leading cause of permanent disability among adults (WHO, 2015). However, the country lacks organized stroke units which makes the status of acute care unclear and questionable. Thus, the current situation in the country urges the need to initiate epidemiological studies to assess stroke care and post-stroke outcomes (mortality, disability, QOL, etc.). Predictors of in-hospital death may also be of a major importance in improving stroke management and prognosis. One retrospective hospital-based study assessed acute stroke care and discharge outcome (Lahoud et al., 2018). Another retrospective study examined patient characteristics and outcomes in addition to barriers to rt-PA utilization in a tertiary care center in Beirut, Lebanon (El Sayed et al., 2014). A hospital-based study evaluated the benefits and impact of ICU therapeutic interventions on the survival and functional ability of severe stroke patients (Riachy et al., 2008).

3. Objectives

Despite stroke high burden in Lebanon, national epidemiological, clinical and socio-economic data on stroke are rare and incomplete in Lebanon, especially prospective ones. Therefore we decided to conduct a multicenter prospective medico-economic cohort study of stroke management in Lebanon.

The aims of this thesis were:

- To assess the current practices of doctors in Lebanon routinely involved in stroke treatment (AIS management).
- To estimate the financial and economic direct in-hospital costs of acute stroke care in Lebanese stroke hospitalized patients (room and board, laboratory, general exams, physicians, drugs, rehabilitation therapy, etc.) from a societal point of view using a bottom-up approach (COI analysis) and to evaluate cost drivers.
- To determine the QOL of stroke patients one year after the stroke incidence and its determinants.
- To compare the results of a generic (SF-36) and specific (SS-QOL) questionnaire tool.
- To determine the post-stroke depression rate (using the GDS-15) and its determinants.
- To calculate the one month and one year survival rates post-stroke and identify mortality predictors.

These objectives were distributed over 4 scientific papers:

- 1- Risk factors and Acute Ischemic Stroke Management in Lebanon: Obstacles and Solutions.
- 2- Mortality and predictors of death post stroke: Data from a multicenter prospective cohort of Lebanese stroke patients.
- 3- Quality of life of 1-year stroke survivors and its predictors: a multicenter prospective cohort study.
- 4- Direct medical cost of hospitalization for acute stroke in Lebanon: a prospective incidence-based multicenter cost-of-illness study.

The meeting of these objectives lead to the main objective of any epidemiological study: to better understand and predict the evolution of a disease and its risk factors in order to improve its primary and secondary prevention and limit its physical / psychic / socio-economic impact on the population.

4. Studies

Stroke units are not yet implemented and studies assessing acute stroke care in Lebanon are lacking. Thus, the first study was conducted to assess the current practices of doctors in acute stroke care and treatment in Lebanese hospitals.

Risk factors and Acute Ischemic Stroke Management in Lebanon: Obstacles and Solutions

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Short title: Acute stroke management in Lebanon

Abstract

Background and Aim

Management of acute stroke varies greatly within and between different countries. This study assesses the current practices of doctors in Lebanon routinely involved in stroke treatment.

Methods

We conducted a prospective observational study that included patients who were hospitalized from August 1, 2015 to July 31, 2016, from 8 different Lebanese hospitals with a diagnosis of acute stroke. Baseline characteristics, diagnostic studies, treatments during hospitalization and at discharge were collected and analyzed.

Results

Two hundred and three strokes were recorded and only one hundred seventy three patients (85%) with ischemic event have been included in the study. The mean age was 69.8 ± 12.7 years. All of the patients had brain imaging (CT scan and or MRI) at admission. All ischemic strokes were managed by neurologist and had a cardiologist consultation.

Hypertension was the most prevalent risk factor (78.6%), followed by current cigarette smoking habit (50.3%), diabetes mellitus (42.8%), hypercholesterolemia (39.9%), previous stroke or TIA (17.3%) and atrial fibrillation (14.7%).

Only 4 patients (2.5% of ischemic strokes) received thrombolytic therapy. More than 89% of patients were discharged on at least one anti-hypertensive drug, 89.2% on statin and 37.6% on anti-diabetic medications.

Conclusion

There are many challenges as well as potentials improvement of stroke care in Lebanon. Reperfusion therapy are still largely underused and remains a major challenge in achieving guideline-based reperfusion goals.

Keywords: Ischemic Stroke; management; Lebanon, cardiovascular risk factors

Introduction

Stroke is a leading cause of death worldwide and continues to cast serious disability on the individual making stroke an important cause of morbidity (1). It constitutes a serious public health problem because stroke, not only affects the victim but also their caregivers, family, and the whole society (2).

In most developed countries, the incidence of stroke is declining perhaps due to better understanding and awareness of its risk factors, but there is also an increase in percentage of survivors of stroke due to a better management of acute stroke and to advances in medical technology and reperfusion therapy in the last decade (3). In fact, prompt and efficacious management of acute stroke is probably the most important determinant of patient outcome as new ideas appear for acute treatment, rehabilitation and secondary prevention (4,5). Therefore, therapeutic nihilism is no longer justified.

Local literature on stroke management published from Lebanon is scarce and not exactly known. The objective of this study is to present the current acute ischemic stroke management in Lebanon, in juxtaposition to that of the developed countries. This will help to find lacunae in management and aid in correction of those lacunae to improve patient care, and thereby improve the patient outcomes in acute stroke management. We also intend to highlight areas for future development and improvement in management.

Methods

This prospective study was conducted in 8 different hospitals in Beirut, over a period of 1-year after approval from the Institutional Ethics Committee. Participants (or their responsible caregivers where not possible) provided written informed consent.

All acute stroke patients over the age of 18 years admitted to each participating hospital from August 2015 with confirmed diagnosis of stroke (confirmed by a neurologist with radiological evidence by either CT scan and/or MRI) were recruited.

Patients who did not want to be the part of the study (negative consent), or those who had a stroke of more than one week were excluded. Patients were also excluded if they were suffering from severe pathologies (cancer, fatal renal, hepatic or respiratory insufficiency), or having a moderate to severe cognitive decline before their stroke.

When a patient confirmed to be a candidate in our study inclusion criteria, the prime investigator (R.A.) was contacted and took responsibility of taking consent, filling up the study proforma, and interviewing the patient.

Study tools

Stroke was defined according to the International Classification of Diseases (10th revision) and Transient Ischemic Attack (TIA) was defined as a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischemia and not associated with cerebral infarction (6).

A structured data form including demographics, characteristics, and diagnostic tests performed was completed for all patients.

At presentation, standardized clinical quantification and assessment of the extent of stroke was done using the National Institute of Health Stroke Scale (NIHSS) (7). Stroke severity was classified as no stroke symptoms (score of 0), mild (score of 1 to 4), moderate (score of 5 to 14), moderate/severe (score of 15 to 20) and severe (score of ≥ 21).

Clinical classification of the ischemic stroke was assessed using the Oxfordshire Community Stroke Project (Bamford classification) (8), and clinical outcome was assessed using modified Rankin Scale (mRS) and Bathel Index (BI) (9).

Patients were classified into 3 groups according to mRS (Independent [0 to 2 points], dependent [3 to 5 points] and dead [6 points]) and to four groups according to BI (Independent [96-100], mild dependence [75-95], moderate dependence [46-74] and severe dependence [0-45]) (10).

Stroke etiology was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (11).

Risk factors assessment

The presence of a previous stroke or a concurrent medical illness was determined by history, physical examination and review of medical records.

Hypertension, diabetes mellitus (type 1 or 2) and dyslipidemia were defined by the use of medications for these conditions at the time of study enrolment or at hospital discharge.

Atrial fibrillation (AF) was defined as reported by the respondent or diagnosed by ECG during hospitalisation. Current smokers were defined as persons who reported smoking at least 100 cigarettes during their lifetime and who, at the time they participated in the study, reported smoking every day or some days. Former smokers were defined as those who have smoked at least 100 cigarettes in their lifetime but who have quit smoking since a minimum of 28 days. A researcher pharmacist did the data collection (12).

Education level and monthly home income, were used as indicators of Socio-Economic Status (SES). Health insurance status was classified as public health insurance and private health insurance.

Outcomes analyzed include in-hospital mortality (excluding patients who transferred out or left against medical advice), ambulatory status at discharge, mRS at discharge, and discharge destination.

Statistical analysis

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corporation, Armonk, NY, USA). Two researchers audited 5% randomly selected questionnaires. Data entry showed high reliability (error rate <1%). Data were presented as means±SDs or as percentages. Student's test for means comparison between two groups (for quantitative variables) and Chi-square test (or exact Fisher) for comparing percentages (for nominal, ordinal and categorical variables) were used. Differences in treatment variables at admission and at discharge between survivors were assessed using McNemar (or exact McNemar). $P \leq 0.05$ indicated statistical significance.

Results

Table 1 shows comparisons of socio demographic/clinical variables in the study (ischemic stroke (IS) vs TIA).

Out of 203 recorded strokes, only one hundred seventy three patients with acute ischemic stroke or TIA were included in this study. The mean age of the study group was 69.8 ± 12.7 years (IS group was 70.3 ± 12.3 while that of the TIA group was 62.3 ± 16.0 years, and the difference was significant ($P = 0.035$)). There were more males than females (60.1%). Hypertension was the most prevalent risk factor (78.6%), followed by current cigarette smoking habit (50.3%),

diabetes mellitus (42.8%), hypercholesterolemia (39.9%), previous stroke or TIA (17.3%) and atrial fibrillation (14.7%). There was no significant difference between the IS group and TIA group except for hypertension and dyslipidemia. Around 80% of the population had a public insurance, 20% were illiterate and more than 60% had a monthly home income less than 1,000 USD. No significant difference was detected between the IS group and TIA group.

Clinical outcomes

Assessment of stroke severity and disability were carried out using NIHSS at presentation and mRS at discharge respectively (**Supplementary file**). The mean NIHSS score and mRS were 9.3 ± 8.6 and 3.3 ± 2.0 respectively. TIA patients had significantly low scores compared to ischemic stroke patients ($P<0.001$). The mean Barthel index were (39.6 ± 39.8) and (61.6 ± 38.1) at admission and at discharge respectively. TIA patients had significantly higher scores compared to ischemic stroke patients ($P<0.001$) (**Supplementary file**). Hospital length of stay in TIA patients was significantly lower than that of ischemic stroke patients, so was the percentage of intensive care unit admission ($P<0.001$ for both). Around 80% of patients were discharged home (100% for TIA patients vs. 78% for ischemic stroke patients $P<0.001$) (**Figure 1**).

Diagnostic tests and medical consultations

All ischemic strokes were managed by neurologist and had a cardiologist consultation. Around 84% of diabetic patients had an endocrinologist consult and around 26% of stroke patients were seen by a physical medicine and rehabilitation.

Cardiac evaluation, brain imaging and cervical vessels studies are shown in Table 2. Brain imaging (CT and/or MRI), brain vessels imaging (CT angiography and/or MRA) and cervical vessels imaging (carotid arteries CT angiography and/or cervical MRA and/or carotid duplex scanning) were done in 100%, 26.6% and 90.2% respectively.

ECG was done for all of patients however only 22.0% of them had a 24-hour (Holter) ECG monitoring done. Almost 95% of patients had a TTE done and 9% of them had a TEE done (**Table 2**).

Lipid panel was done for half of the patients. No significant difference was detected between the IS group and TIA group regarding diagnostic tests performed and medical consultation in patients. Only 2.5% of ischemic stroke patients had a venous thrombolytic therapy (**Table 2**).

Exactly 28% of ischemic stroke patients (around 40% of patients with left and/or right arm and/or leg weakness) received in-hospital physical rehabilitation by a physiotherapist (**Table 2**). Only one (1.6%) of the 62 (38.5%) aphasic patients had a speech therapy specialist visit.

Treatments

Comparing treatment prior to the ictus and at discharge we found overall 47.9 % were taking antiplatelet drugs, 14.5% anticoagulants, 39.9 % statins and 78.6% antihypertensive prior to the ictus and 73.5 %, 32.4 %, 89.2 % and 89.2% respectively at discharge ($P<0.001$) (**Table 3**).

Insurance status and SES influence on diagnostic tests performed and medical consultations

When comparing stroke management between public and private Third Party Payer (TPP), no statistical significance was detected except for the 24-hour (Holter) ECG monitoring. Around 40% of patients with private TPP had the 24-hour (Holter) ECG monitoring done vs. 18% only for public TPP ($P=0.01$) (**Table 4**).

Incomplete and negative evaluation on TOAST classification

When comparing stroke management between SES, low and middle SES patients had more brain CT done compared to high SES patients ($P=0.020$), these latter had more brain MRI done but the difference tended to be significant ($P=0.063$). However, middle and high SES had significantly more brain MRA done ($P=0.005$) (**Table 4**).

All patients with incomplete evaluation on TOAST classification ($n=23$) had neurologist and cardiologist consults and a brain CT and/or MRI and ECG done. Cervical MRA and/or carotid duplex scanning and TTE (with or without TEE), were done in 91.3% ($n=21$) and 95.7% ($n=22$) respectively. However, 24-hour (Holter) ECG monitoring wasn't done to any of the 23 patients.

All patients with negative evaluation on TOAST classification ($n=17$) had neurologist and cardiologist consults and a brain CT and/or MRI, ECG, 24-hour (Halter) ECG monitoring, cervical MRA and/or carotid duplex scanning and TTE (with or without TEE) done.

Discussion

The current study conducted on 173 patients presented with acute ischemic stroke or TIA provides a unique opportunity to study risk factors, and acute management of stroke in Lebanon.

The mean age of our patient population was around 70 years, which is compared with European registries and markedly higher compared with Middle East where clinical series showed a mean age of stroke within the sixth and seventh decade **(14)**. Furthermore, as could be expected this study showed higher male prevalence (60%) than females in ischemic stroke. This higher prevalence can be explained by the hormonal constitutional factors, the higher rate of smoking and modifiable risk factors in men and a higher rate of stressful situations among males than females **(15)**.

Among the modifiable risk factors, arterial hypertension is considered the most important for cerebrovascular accident and is one of the most prevalent cardiovascular risk factors. In fact, the risk for stroke increases progressively with incremental increases in blood pressure as shown in numerous epidemiologic studies **(16,17)**. In the present study, hypertension was the most common risk factor for ischemic stroke, which was detected in 78 % of all studied cases which is slightly higher than the prevalence reported in several studies from Arab and European countries **(15,18,19)**.

In our study, diabetes mellitus was recorded in 42% of patients. It is slightly lower than the prevalence reported in different Arab countries where diabetes mellitus was recorded in 55 % of patients **(14)** and slightly higher than in several occidental countries **(15,19)**.

Smoking was recorded in mostly half of the patients and dyslipidemia in 40% of all patients which is higher than those reported from other studies from the region **(15)** and from low to middle income countries **(20)**. Even though most people who smoke are aware that smoking damage health, lack of awareness campaigns and programmes towards the dangers of smoking on vessels in our country explain this high smoking rate in our study.

Our study showed that, the diagnostic approach to acute stroke in Lebanon was consistent with international recommendations **(13)**. In fact, all stroke patients (100%) had documented brain imaging during their hospital stay within 24h and 75% of them had a brain MRI, which confirm the diagnosis of ischemic stroke vs. TIA. Severe stroke and agitation were the most frequent reason for not doing MRI. Unfortunately, the registry did not collect the exact timing of patients presentation to the emergency room and CT scans, thus we were unable to determine the proportion of patients scanned within 0–4.5h of symptom onset. However we believe that there is a delayed hospital presentation for stroke patients which explain in part the small percentage of patients treated with venous thrombolytic in our study (2.5%). In addition, lack of public awareness and knowledge about stroke symptoms and the absence of an organized and

comprehensive stroke program in the Lebanese hospitals are the biggest obstacles to receiving proper acute stroke treatment.

During the study period, a high percentage of patients were documented as having received cardiac work up, cervical vessels imaging and the specialist consultations recommended by several international practice guidelines as part of routine ischemic stroke care **(21)**.

Even though all patients with incomplete evaluation on TOAST classification had an ECG done, none of them did 24-hour Holter monitoring. The ideal method for the determination of AF, a risk factor for ischemic stroke or TIAs **(22)**, in patients with stroke is not known **(23)**. A single ECG recording upon presentation with stroke was shown to detect a new diagnosis of AF in 2% to 3% of patients **(24)**. Holter monitoring has been used in several stroke units to identify potentially underdiagnosed AF. It has been suggested that every additional 24 hours of monitoring detects previously undiagnosed AF in an additional 2% to 4% of patients **(24)**. However, a very high percentage of asymptomatic patients remain undiagnosed leading to a potential risk of thromboembolism **(25)**. Considering that a significant risk reduction can be achieved by oral anticoagulants, identifying AF is clinically relevant **(26)**.

For patients with a negative evaluation on TOAST classification, prolonged rhythm monitoring (in addition to Holter) might detect a cardioembolic cause and reduce this number. In fact, it was shown to be useful for the detection of AF after cryptogenic stroke **(27,28)**. This suggests a substantial number of undiagnosed patients despite screening by 24-hour Holter monitoring. Furthermore, a review found that 24- to 72- hour Holter monitoring detected 4.6% of consecutive patients with IS **(29)**. Prolonging to 72- hour Holter monitoring might detect more AF stroke etiology.

In addition, numerous studies have indicated that health insurance can reduce disparities in access to care and health outcomes **(30,31)**. Studies have also reported that insurance status and lower SES are independent indicators of stroke outcome **(32,33)**. We did not find any relation between insurance status and the management of stroke except that private TPP had higher number of 24-hour (Holter) ECG monitoring. Only higher SES was positively correlated to a higher number of MRI. These findings might be partly explained by the fact that our study was done in Beirut (urban area) and it is known that rural populations have lower access to healthcare and a higher economic burden than urban residents.

Finally, in line with several studies (34-36) and in accordance with international recommendations (6), we found a high percentage of medication prescriptions for our patients at discharge regarding the control of their modifiable risk factors including blood pressure, diabetes mellitus, dyslipidemia, antiplatelet and anticoagulant prescription.

The small sample size in this study is a major limitation. It is however important to mention that all stroke patients during the study period were approached and more than 90% of them participated to the study. Another limitation of this study is that it was conducted only in Beirut. Therefore, some of our results may not be generalizable to other regions of Lebanon. A larger multicenter study covering the whole geographic area of Lebanon is recommended. However, despite these limitations, this study produced important epidemiological data regarding stroke patient's risk factor and acute stroke management.

Conclusion

Despite overall good adherence to diagnostic evidence-based and clinical practice guidelines reperfusion therapy are still largely underused and remains a major challenge in achieving guideline-based reperfusion goals. It is therefore essential that patients be aware of the symptoms of stroke, as well as the importance of presenting immediately to a medical facility from the time of symptom onset for evaluation and subsequent rapid and appropriate management.

The implementation of stroke unit at the hospitals, as well as stroke management protocols, will be important steps toward improving the standard of care.

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Conflicts of interest

All authors declare that they have no conflict of interest.

Table 1: Demographics and risk factors

	Both IS+TIA (n=173;100%)	IS (n=161;93.1%)	TIA (n=12;6.9%)	P-value
Age (mean±SD)	69.8±12.7	70.3±12.3	62.3±16.0	0.035
Gender–Male (n (%))	104(60.1%)	96(59.6%)	8(66.7%)	NS
Risk factors				
-Hypertension	136(78.6%)	126(78.3%)	10(83.3%)	0.020
-Dyslipidemia	69(39.9%)	60(37.3%)	9(75.0%)	0.014
-Diabetes Mellitus	74(42.8%)	70(43.5%)	4(33.3%)	NS
-Atrial Fibrillation	25(14.5%)	22(13.7%)	3(25.0%)	NS
-Smoker				NS*
▪ former smoker	27(15.6%)	24(14.9%)	3(25.0%)	
▪ current smoker	87(50.3%)	82(50.9%)	5(41.7%)	
Previous stroke/TIA	30(17.3%)	29(18.0%)	1(8.3%)	NS
TPP				NS
Public	140(80.9%)	129(80.1%)	11(91.7%)	
Private	33(19.1%)	32(19.9%)	1(8.3%)	
Education				NS*
Illiterate	35(20.2%)	34(21.1%)	1(8.3%)	
Elementary	71(41.0%)	67(41.6%)	4(33.3%)	
Secondary	31(17.9%)	27(16.8%)	4(33.3%)	
≥High school	36(20.8%)	33(20.5%)	3(25.0%)	
Monthly home income (USD)				NS*
<500	54(31.2%)	52(32.3%)	2(16.7%)	
[500-1,000[53(30.6%)	48(29.8%)	5(41.7%)	
[1,000-1,500]	28(16.2%)	26(16.1%)	2(16.7%)	
>1,500	38(22.0%)	35(21.7%)	3(25.0%)	

*Non parametric tests used.

IS= ischemic stroke; TIA= transient ischemic attack; TPP= third party payer.

Supplementary file

	Both IS+TIA (n=173;100%)	IS (n=161;93.1%)	TIA (n=12;6.9%)	P-value
NIHSS on admission	9.3±8.6	10.0±8.6	0.7±1.0	<0.001
No stroke symptom	10(5.8%)	3(1.9%)	7(58.3%)	
Minor stroke	59(34.1%)	54(33.5%)	5(41.7%)	
Moderate stroke	63(36.4%)	63(39.1%)	0(0.0%)	<0.001*
Moderate/severe stroke	17(9.8%)	17(10.6%)	0(0.0%)	
Severe stroke	24(13.9%)	24(14.9%)	0(0.0%)	
BI at admission	39.6±39.8	36.9±39.3	77.1±25.4	<0.001
LOS	9.4±8.7	9.9±8.8	3.4±1.6	<0.001
ICU admission	79(45.7%)	78(48.4%)	1(8.3%)	<0.001
ICU LOS	3.3±6.6	3.6±6.8	0.2±0.6	<0.001
mRS at discharge	3.3±2.0	3.5±1.9	0.6±0.9	<0.001
No symptoms	22(12.7%)	15(9.3%)	7(58.3%)	
No significant disability	24(13.9%)	20(12.4%)	4(33.3%)	
Slight disability	11(6.4%)	11(6.8%)	0(0.0%)	
Moderate disability	26(15.0%)	25(15.5%)	1(8.3%)	<0.001*
Moderate severe disability	27(15.6%)	27(16.8%)	0(0.0%)	
Severe disability	43(24.9%)	43(26.7%)	0(0.0%)	
Dead	20(11.6%)	20(12.4%)	0(0.0%)	
BI at discharge	61.6±38.1	58.5±38.1	97.9±4.5	<0.001
Independence	46(26.6%)	37(26.2%)	9(75.0%)	
Mild dependence	30(17.3%)	27(19.1%)	3(25.0%)	<0.001*
Moderate dependence	26(15.0%)	26(18.4%)	0(0.0%)	
Severe dependence	51(29.5%)	51(36.2%)	0(0.0%)	
Discharge destination				<0.001*
Home	68(39.3%)	56(34.8%)	12(100%)	
Home with help	69(39.9%)	69(42.9%)	0(0%)	
Rehabilitation center/ Nursing home	16(9.2%)	16(9.9%)	0(0%)	
Death	20(11.6%)	20(12.4%)	0(0%)	
TOAST classification				0.014
LA	37(21.4%)	36(22.4%)	1(8.3%)	
CE	55(31.8%)	53(32.9%)	2(16.7%)	
SV	27(15.6%)	27(16.8%)	0(0%)	
UC	54(31.2%)	45(27.9%)	9(75.0%)	0.017*
- Rare other causes	1 (0.6%)	1 (0.6%)	0 (0%)	
- ≥ 2 causes	4 (2.3%)	4 (2.5%)	0 (0%)	
- NE	19 (11.0%)	17 (10.6%)	2 (16.7%)	
- IE	30 (17.3%)	23 (14.3%)	7 (58.3%)	

*Non parametric tests used.

(mean±SD)

IS= ischemic stroke; TIA= transient ischemic attack; LOS= length of stay; ICU= intensive care unit; NIHSS= National Institution of Health Stroke Scale; mRS= modified Rankin Scale; BI= Barthel Index; TOAST= Trial of Org 10172 in Acute Stroke Treatment; LA= large-artery atherosclerosis; CE= cardioembolism; SV= small-vessel occlusion; UC= unclassified; NE= negative evaluation; IE= incomplete evaluation

Table 2: Diagnostic tests performed and medical consultation in patients with ischemic event

	Both IS+TIA (n=173;100%)	IS (n=161;93.1%)	TIA (n=12;6.9%)	P-value
Brain imaging (CT and/or MRI)	173(100%)	161(100%)	12(100%)	NS
•Brain CT	138(79.8%)	130(80.7%)	8(66.7%)	NS
•Brain MRI	135(75.0%)	126(78.3%)	9(75.0%)	NS
Brain vessels imaging	46(26.6%)	43(26.7%)	3(25.0%)	NS
•Brain CT angiography	5(2.9%)	5(3.1%)	0(0.0%)	NS*
•Brain MRA	44(25.4%)	41(25.5%)	3(25.0%)	NS
Cervical vessels imaging	150(86.7%)	138(85.7%)	12(100%)	NS
•Carotidarteries CT angiography	5(2.9%)	5(3.1%)	0(0.0%)	NS*
•Cervical MRA	16(9.2%)	16(9.9%)	0(0.0%)	NS*
•Carotid duplex scanning	145(83.8%)	133(82.6%)	12(100%)	NS
TEE	15(8.7%)	14(8.7%)	1(8.3%)	NS
TTE	164(94.8%)	153(95.0%)	11(91.7%)	NS
ECG	171(98.8%)	159(98.8%)	12(100%)	NS*
Lipid panel	88(50.9%)	84(52.2%)	4(33.3%)	NS
24-hour Holter monitoring	38(22.0%)	37(23.0%)	1(8.3%)	NS
Physical rehabilitation	45(26.0%)	45(28.0%)	0(0.0%)	0.033
Neurologist	172(99.4%)	161(100%)	11(91.7%)	NS*
Cardiologist	171(98.8%)	160(99.4%)	11(91.7%)	NS*
Endocrinologist	43(24.9%)	41(25.5%)	2(16.7%)	NS
Thrombolytic therapy	-	4(2.5%)	-	-

*Non parametric tests used.

IS= ischemic stroke; TIA= transient ischemic attack.

Table 3: Treatments at admission and at discharge

	All (n=173;100%)			IS (n=161;93.1%)		
	Admission	Discharge	P-value	Admission	Discharge	P-value
HT therapy	136(78.6%)	132(89.2%)	<0.001	126(78.3%)	122(89.7%)	<0.001
DL therapy	69(39.9%)	132(89.2%)	<0.001	60(37.3%)	123(90.4%)	<0.001
DM therapy	74(42.8%)	56(37.6%)	NS (0.065)	70(43.5%)	53(38.7%)	NS
AP therapy	79(47.9%)	108(73.5%)	<0.001	75(48.7%)	100(74.1%)	<0.001
AF therapy	25(14.5%)	48(32.4%)	<0.001	22(13.7%)	45(33.1%)	<0.001
AD therapy	21(12.1%)	14(9.5%)	NS	20(12.4%)	13(9.6%)	NS

HT= hypertension; DL= dyslipidemia; DM= diabetes mellitus; AP= antiplatelet; AF= atrial fibrillation; AD = antidepressant.

Table 4: Diagnostic tests performed and medical consultations by insurance status and SES

	Both IS+TIA (n=173;100%)							
	Private 33(19.1%)	TPP Public 140(80.9%)	P-value	<500 54(31.2%)	[500-1000[53(30.6%)	SES (USD) [1000-1500[28(16.2%)	≥1500 38(22.0%)	P-value
Brain CT	23(69.7%)	115(82.1%)	NS	43(79.6%)	47(88.7%)	24(85.7%)	24(63.2%)	0.020
Brain MRI								
-With contrast	2(6.1%)	22(15.7%)	NS	9(16.7%)	8(15.1%)	2(7.1%)	5(13.2%)	NS
-Without contrast	27(81.8%)	108(77.1%)	NS	43(79.6%)	37(69.8%)	20(71.4%)	35(92.1%)	NS (0.063)
Brain MRA	8(24.2%)	36(25.7%)	NS	9(16.7%)	8(15.1%)	14(50.0%)	13(34.2%)	0.001
Cervical MRA	4(12.1%)	12(8.6%)	NS	5(9.3%)	3(5.7%)	3(10.7%)	5(13.2%)	NS*
Carotid duplex scanning	29(87.9%)	116(82.9%)	NS	47(87.0%)	47(88.7%)	26(92.9%)	31(81.6%)	NS
TEE	4(12.1%)	11(7.9%)	NS	3(5.6%)	4(7.5%)	3(10.7%)	5(13.2%)	NS*
TTE	32(97.0%)	132(94.3%)	NS	52(96.3%)	51(96.2%)	26(92.9%)	35(92.1%)	NS*
ECG	33(100%)	138(98.6%)	NS*	54(100%)	53(100%)	28(100%)	38(100%)	NS*
Lipid panel	18(54.5%)	70(50.0%)	NS	27(50.0%)	30(56.6%)	13(46.4%)	18(47.4%)	NS
24-hour Holter	13(39.4%)	25(17.9%)	0.010	10(18.5%)	14(26.4%)	5(17.9%)	9(23.7%)	NS
Neurologist	33(100%)	139(99.3%)	NS*	55(100%)	52(98.1%)	28(100%)	38(100%)	NS*
Cardiologist	32(97.0%)	139(99.3%)	NS*	54(100%)	52(98.1%)	28(100%)	37(97.4%)	NS*
Endocrinologist	6(24.9%)	37(26.4%)	NS	9(16.7%)	13(24.5%)	8(28.6%)	13(34.2%)	NS

*Non parametric tests used.

IS= ischemic stroke; TIA= transient ischemic attack; TPP= third party payer; SES= socioeconomic status

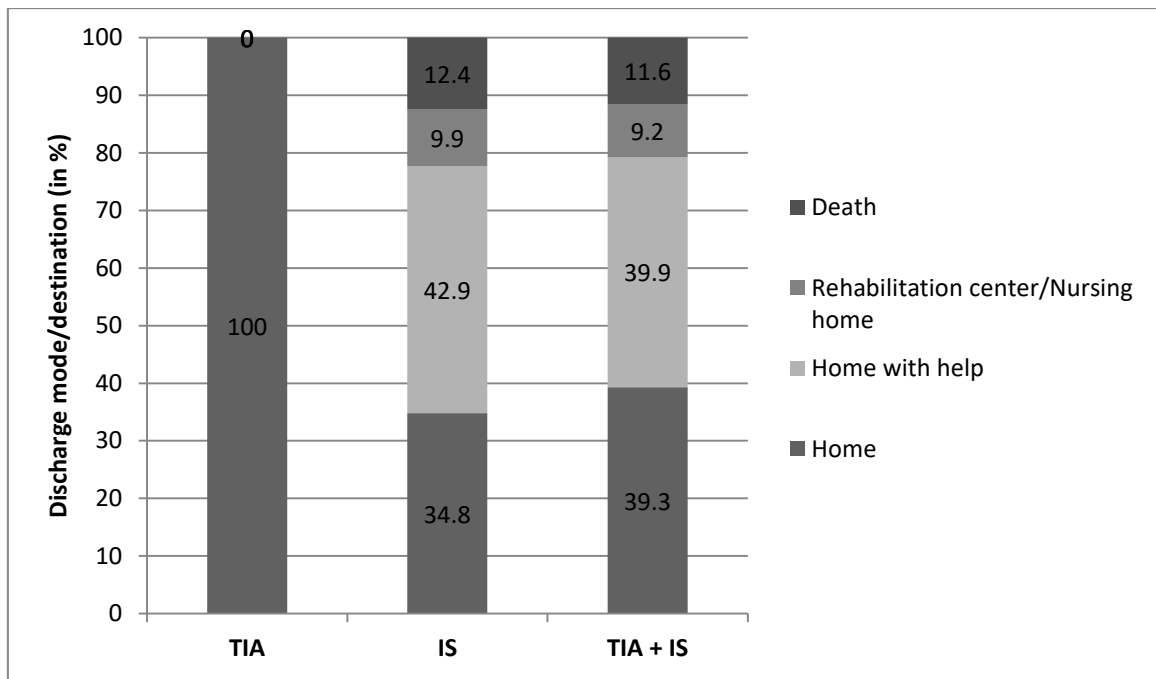


Figure 1: Discharge mode/destination

References

1. Stroke research: closing the gap between evidence and practice. *Lancet Neurol.* 2012;11:11-21.
2. Haley WE, Allen JY, Grant JS, et al. Problems and Benefits Reported by Stroke Family Caregivers: Results from a Prospective Epidemiological Study. *Stroke; a journal of cerebral circulation.* 2009;40(6):2129-2133.
3. Vuong SM, Carroll CP, Tackla RD, et al. Application of emerging technologies to improve access to ischemic stroke care, *Neurosurg Focus.* 2017 Apr;42(4)
4. Taylor TN, Davis PH, Torner JC, et al. Lifetime cost of stroke in the United States. *Stroke.* 1996;27:1459–66.
5. Davis S, Lees K, Donnan G. Treating the acute stroke patient as an emergency: current practices and future opportunities. *International Journal of Clinical Practice.* 2006;60(4):399-407.
6. Easton JD, Saver JL, Albers GW, et al. American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery

and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009 Jun;40(6):2276-93.

7. The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1998;28:2119–25.

8. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521–6.

9. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke*. 1999;30(8):1538-41.

10. Fattore G, Torbica A, Susi A, et al. The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC Neurol*. 2012;12(1):137.

11. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.

12. Centers for Disease Control and Prevention (CDC). Smoking & Tobacco Use. Available at: <https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm> (Accessed on 09 Jul 2017)

13. Powers WJ, Rabinstein AA, Ackerson T, et al. American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018 Mar;49(3)

14. Benamer HT, Grosset D. Stroke in Arab countries: a systematic literature review. *J Neurol Sci*. 2009 Sep 15;284(1-2)

15. Abboud H, Sissani L, Labreuche J, et al. OPTIC Registry and PERFORM Trial Investigators. Specificities of Ischemic Stroke Risk Factors in Arab-Speaking Countries. *Cerebrovasc Dis*. 2017;43(3-4):169-177

16. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903.

17. Pastor-Barriuso R, Banegas JR, Damián J, Appel LJ, Guallar E Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. *Ann Intern Med*. 2003;139(9):731.

18. Deleu D, Inshasi J, Akhtar N, et al. Risk factors, management and outcome of subtypes of ischemic stroke: a stroke registry from the Arabian Gulf. *J Neurol Sci.* 2011 Jan 15;300(1-2):142-7.
19. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001 Sep 29;358(9287):1033-41. Erratum in: *Lancet.* 2001 Nov 3;358(9292):1556.
20. Abboud H, Labreuche J, Arauz A, et al. OPTIC Registry Investigators. Demographics, socio-economic characteristics, and risk factor prevalence in patients with non-cardioembolic ischaemic stroke in low- and middle-income countries: the OPTIC registry. *Int J Stroke.* 2013 Oct;8
21. National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. 2008 Available at: <<http://nice.org.uk/guidance/cg68>>. (Accessed 18 Dec 2015).
22. Hart RG. Stroke prevention in atrial fibrillation. *Curr Cardiol Rep.* 2000;2(1):51-55.
23. Orrsjo G, Cederin B, Bertholds E, et al. Screening of paroxysmal atrial fibrillation after ischemic stroke: 48-hour Holter monitoring versus prolonged intermittent ECG recording. *ISRN Stroke.* 2014;2014:6.
24. Kamel H, Smith WS. Detection of atrial fibrillation and secondary stroke prevention using telemetry and ambulatory cardiac monitoring. *Curr Atheroscler Rep.* 2011;13(4):338-343.
25. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol.* 1994;74(3):236-241.
26. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet.* 1993;342(8882):1255-1262.
27. Sanna T, Diener HC, Passman RS, Crystal et al. Cryptogenic stroke and atrial fibrillation. *N Engl J Med.* 2014;371(13):1261.
28. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med.* 2014;370(26):2467-2477.
29. Liao J, Khalid Z, Scallan C, et al. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke.* 2007;38(11):2935-2940.
30. Levy H, Meltzer D. The impact of health insurance on health. *Annu Rev Public Health.* 2008;29:399-409.

31. Freeman JD, Kadiyala S, Bell JF, et al. The causal effect of health insurance on utilization and outcomes in adults: a systematic review of US studies. *Med Care*. 2008;46:1023–32.
32. McManus M, Ovbiagele B, Markovic D, et al. Association of Insurance Status with Stroke-Related Mortality and Long-term Survival after Stroke. *J Stroke Cerebrovasc Dis*. 2015;24:1924–30.
33. Addo J, Ayerbe L, Mohan KM, et al. Socioeconomic status and stroke: an updated review. *Stroke*. 2012;43:1186–91.
34. Amarenco P, Labreuche J, Touboul PJ. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. *Atherosclerosis*. 2008 Feb;196(2):489-96.
35. Chapman N, Huxley R, Anderson C, et al. Writing Committee for the PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke*. 2004 Jan;35(1):116-21
36. Shulga O, Bornstein N. “Antiplatelets in Secondary Stroke Prevention.” *Frontiers in Neurology* 2 (2011): 36. PMC. Web. 8 Sept. 2018.

The first study sheds the light on the critical situation of acute stroke care in Lebanese hospitals, and the need to implement organized stroke units to improve stroke patients' acute management. Public awareness campaigns on stroke symptoms, risk factors and the time-dependent nature of the disease may help patients arrive earlier to hospitals, before severe brain damage occurs. The current situation in the country urges the need to initiate epidemiological studies to assess post-stroke outcomes. Predictors of short-term and long-term mortality may also be of a major importance in improving stroke management and prognosis. Therefore, the second study was conducted to examine mortality rates during the first year after acute stroke and the major short-term (1-month) and long-term (1-year) mortality predictors.

Mortality and predictors of death post stroke: Data from a multicenter prospective cohort of Lebanese stroke patients

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Short title: Mortality and predictors of death post stroke in Lebanon

Abstract

Background: Despite efforts to reduce stroke mortality rates, the disease remains a leading cause of death in Lebanon highlighting the importance of understanding risk factors and subsequent mortality. We examined mortality rates during the first year after acute stroke and the major short-term (1-month) and long-term (1-year) mortality predictors.

Methods: Data were collected prospectively on hospitalized stroke patients from eight hospitals in Beirut during a 1-year period. Patients were followed up for 1-year or until death. Mortality rates were assessed at 1-month and at 1-year post stroke and predictors of death were evaluated using Cox proportional hazard model.

Results: A total of 203 stroke patients were included. Survival data were completed for over 97% of patients. Cumulative mortality rates were 13.3% at 1-month and 21.2% at 1-year. Predictors of short-term and long-term mortality in univariate analysis were low socioeconomic status, intensive care unit admission, decreased level of consciousness, stroke severity and presence of complications. Marital status also predicted short-term mortality, while age >64 years and surgery need were also long-term mortality predictors. In multivariate analysis, stroke severity and presence of complications were predictors of death at 1-month and at 1-year. Low socioeconomic status, dependency in daily living activities, and the presence of co-morbidities were additional predictors of 1-year mortality.

Conclusion: Approximately one over five of patients did not survive 1-year after stroke. There is a need for aggressive intervention to improve stroke knowledge, warning and prevention which may reduce this high stroke mortality rate in Lebanon.

Keywords: Stroke; mortality; predictors; short-term; long-term; Lebanon

Introduction

Stroke is the third leading cause of death⁽¹⁾ with an annual 6 million fatal events worldwide.⁽²⁾ Most of these stroke deaths are found in the developing countries and account for as much as 87% of all the stroke deaths.⁽³⁾

According to the WHO, 15 million people suffer stroke worldwide each year. Of these, 5 million die, and another 5 million are left permanently disabled.⁽⁴⁾

The prognosis after acute stroke varies greatly in individual patients, depending on stroke severity, stroke characteristics (location and size) and on the patient's premorbid condition, age and post-stroke complications.⁽⁵⁾ In fact, post-stroke complication is a leading cause of death accounting for 23–50% of total deaths in patients with ischemic stroke.⁽⁶⁾

Stroke mortality is an important outcome measure in stroke epidemiology studies and clinical trials, and data on stroke mortality are critical for monitoring disease trends and planning public health interventions. Furthermore, identifying predictors of mortality after acute stroke is of paramount importance for clinicians, so that specific therapies and management strategies can be applied to patients at high risk of dying with a consequent reduction in stroke mortality and disability.

There is paucity in literature in regards to the data about stroke mortality due to a lack of studies in Lebanon.⁽⁷⁾ The aim of this study was to investigate the stroke mortality rates and examine its major potential predictors of short-term and long-term mortality in a multicenter hospital-based cohort of Lebanese stroke patients.

Methods

The ethical committees of all the participating hospitals approved the study. Participants (or their responsible caregivers where not possible) provided written informed consent.

Study design

Stroke patients aged ≥ 18 years, admitted during 1-year period from August 2015 in 8 different hospitals in Beirut were included prospectively in this study and followed up for one year or until death. Stroke was defined according to the International Classification of Diseases (10th revision) including subarachnoid hemorrhage, intracerebral hemorrhage and cerebral infarction; Transient Ischemic Attack (TIA) was defined as a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischemia and not associated with cerebral infarction.⁽⁸⁾ Patients admitted after seven days of symptoms onset or those who had difficulty accepting follow-up visits were excluded. Patients were also excluded if they were suffering from severe pathologies with unfavorable 1-year prognosis (cancer, fatal renal, hepatic or respiratory insufficiency), or having a moderate to severe cognitive decline before their stroke.

Study tools

A structured data form including demographics, characteristics, and diagnostic tests performed was completed for all patients. Stroke severity on admission was assessed with the National Institute of Health Stroke Scale (NIHSS)⁽⁹⁾ and classified as no stroke symptoms (score of 0), mild (score of 1 to 4), moderate (score of 5 to 14), moderate/severe (score of 15–20) and severe (score of ≥ 21). Clinical classification of the ischemic stroke was assessed using the Oxfordshire Community Stroke Project (Bamford classification)⁽¹⁰⁾, and clinical outcome was assessed using modified Rankin Scale (mRS).⁽¹¹⁾ Patients were classified into 3 groups according to mRS (Independent [0 to 2 points], dependent [3 to 5 points] and dead [6 points]) and to four groups according to BI (Independent [96-100], mild dependence [75-95], moderate dependence [46-74] and severe dependence [0-45]).⁽¹²⁾ Stroke etiology was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.⁽¹³⁾

Mortality rates were prospectively assessed at 1-month, during the follow-up period and at 12-months post-stroke by regular home visits.

Risk factors assessment

The presence of a previous stroke was determined on the basis of history and review of medical records. The existence of concurrent medical illness was determined by history, physical examination, laboratory data, and review of medical records. Risk factors such as hypertension, diabetes mellitus (type 1 or 2), dyslipidemia and atrial fibrillation were defined by the use of medications for these conditions at the time of study enrolment or at hospital discharge. The data for baseline information on smoking status were also collected.

Education level, employment status and monthly personal income were used as indicators of Socio-Economic Status (SES).

Statistical analysis

Cumulative mortality rates at 1-month and 1-year follow-ups were calculated for all stroke patients. Differences in baseline variables between survivors, non-survivors and lost to follow up at 1-year after the stroke were assessed with the χ^2 test (or exact Fisher) for proportions and ANOVA (analysis of variance) test (or Kruskal Wallis) for between-group comparison. Determinants of death were evaluated using the Cox proportional hazard model at 1-month, 1-year and overall death. Univariate associations between mortality and each of the individual variables that were identified as possible predictors of mortality were assessed using Kaplan–Meier survival analysis and significance determined using the log rank test. The identified predictors with a univariate $p < 0.2$ were subjected to multivariate Cox regression analyses using forward stepwise selection. Hazard ratios for mortality were determined by univariate and multivariate Cox proportional hazards regression analyses, with data presented as hazard ratio with 95% CIs. Log minus log plots were evaluated to test the validity of the proportionality of hazards assumption over time; all variables met this assumption. The Kaplan-Meier mortality curves at 1-month, 1-year and overall mortality were presented. At 1-year follow-up, data

analysis was conducted only for 1-month survivors. The P-value of ≤ 0.05 was considered statistically significant. Analyses were performed with the SPSS 21.0 software.

Results

Two hundred and three patients were included in this study (approximately 5% of patients did not give their written consent and were therefore excluded from the study); the mean age was 69 ± 13 years and 58% were men (Table 1). Survival data during the study period were complete for over 97% of patients. No significant difference was observed between lost to follow up and followed up patients concerning socio-demographic and clinical characteristics (Tables 1 and 2).

Cumulative rates of mortality were 13.3% at 1-month and 21.2% at 1-year follow-up. The risk of death was highest in the first month. For 1-month survivors, the mortality rate during 3, 6 and 12 months after the stroke was approximately 4.5%, 1.2% and 3.0% respectively. Fifteen of the 176 survivors at 1-month (8.5%) did not survive at 1-year after the stroke. Mortality curves at 1-month, 1-year (for 1-month survivors only) and overall mortality are shown in the figures 1-A, 1-B and 1-C.

Table 1 presents the socio-demographic characteristics of the study population according to survival status at 1-month and 1-year. Survivors at 1-month (86.7%) and at 1-year (78.8%) were significantly younger than the deceased (mean age: 68 ± 13 years for 1-month survivors vs. 77 ± 12 for 1-month deceased, $p=0.001$; 67 ± 12 years for 1-year survivors vs. 76 ± 12 for 1-year deceased, $p<0.001$). Gender, education and living status were not statistically significant factors for mortality. However, the proportion of 1-month deceased patients was significantly lower among married patients, compared with single/divorced/widowed patients ($p=0.027$). Higher 1-month and 1-year death occurred in housewife and unemployed patients compared to employed and retired patients ($p=0.044$ and 0.004 respectively) and in patients with low

monthly personal income compared to high monthly personal income ($p=0.034$ and 0.012 respectively).

Table 2 presents the clinical characteristics of the patients by survival status at 1-month and 1-year. No statistically significant difference was noted between survivors and non-survivors regarding stroke types. Hypertension was the only risk factor statistically significant between survivors and non-survivors for mortality at 1-year ($p=0.012$). No statistically significant difference was observed for other common risk factors such as diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, recurrent stroke and smoking. Stroke severity and infectious complications were significantly associated to mortality at one and 12 months ($p<0.001$). Among 1-month survivors, mRS was significantly lower and BI was significantly higher among alive patients compared to deceased at 1-year. Cardio-embolic stroke had the highest mortality rate between ischemic strokes and the highest mortality rates were found for patients with partial anterior circulation stroke.

Variables identified in the univariate survival analysis as independent predictors of death at 1-month, 1-year and overall mortality are presented in table 3. Decreased level of consciousness, high NIHSS score and the presence of infectious complications were predictors of 1-month, 1-year and overall mortality. Marital status, low monthly personal income and intensive care unit (ICU) admission were additional 1-month mortality predictors. High mRS, low BI score, surgery needed and the presence of co-morbid conditions such as recurrent stroke and atrial fibrillation were additional 1-year mortality predictors. Additional predictors of overall mortality were age >64 years, low monthly personal income, employment status, ICU admission, surgery needed and the presence of hypertension as a co-morbid condition.

Variables identified in the multivariate survival analysis as independent predictors of death at 1-month, 1-year and overall mortality are presented in table 4. Stroke severity and infectious complication occurrence were predictors of death at 1-month (HR=2.0, $p=0.003$; HR=4.2,

p=0.013 respectively) and overall death (HR=2.0, p<0.001; HR=4.1, p=0.001 respectively); however, disability in daily living activities (low BI score HR=0.14, p=0.002), atrial fibrillation (HR=4.6, p=0.035) and recurrent stroke (HR=4.7, p=0.023) were additional predictors of long-term mortality for patients alive 1-month post stroke.

Considering housewives as reference, unemployed patients had a higher mortality rate and employed or retired patients had a lower mortality rate (p=0.003).

Discussion

This prospective study was designed to find out both short- and long- term stroke mortality and their major determinants in hospitalized patients followed up for a year after an acute stroke.

Cumulative mortality rates for stroke patients increased from approximately one over eight at 1-month to one over five 1-year after the event. Almost one over twelve of survivors at 1-month did not survive at 1-year. In addition we found that the first two weeks after stroke onset comprise a critical period for stroke patients since 12% and 31% died within the first and second week respectively. The non-survivor's percentage increased after the first two weeks getting to 64% by the end of thirty days. Our findings are not surprising. A Canadian study reported close 30-day and 1-year mortality rates after stroke of 13% and 24% respectively⁽¹⁴⁾ which are consistent with our findings. However prior studies have reported lower 1-month and 1-year mortality rates⁽¹⁵⁻¹⁶⁾ while others reported a slightly higher rates than ours.⁽¹⁷⁻¹⁸⁾

Several factors are known to influence short- and long -term mortality. As expected, we found that initial stroke severity and infectious complications were independent determinants of short- and long-term mortality. Our findings support previous reports where stroke severity^(14,16,19-21) and infectious complications^(7,14,21-22) were independent strong predictor of short- and long-term mortality. Therefore, reducing stroke severity and the risk of infection will therefore be paramount in curtailing the mortality rate. Patients with initial stroke severity or higher risk for

infection may benefit from early treatment, preventative interventions and sooner outpatient follow-up.

Recurrent stroke, hypertension and atrial fibrillation are positively associated with post-stroke death and this is consistent with previous studies.⁽²³⁻²⁵⁾ Therefore, improved control of these factors can potentially prevent part of stroke mortality. International guidelines for management of stroke recommend optimal management of vascular risk factors as part of the secondary prevention treatment.⁽²⁶⁾ Efforts should be also done on primary prevention measures with emphasis mainly on more aggressive control of risk factors, especially that they are modifiable risk factors, in order to reduce stroke incidence and therefore stroke mortality.

Patients having a higher BI (being independent in DLA) were significantly more likely to survive than those with a lower score. In fact, as proven in other studies⁽²⁷⁾, BI is a useful predictor for 1-year mortality and being dependent in DLA increase the long-term mortality rate.

Unemployed patients had lower survival rate compared to the reference while employed patients had higher survival rate compared to the reference. Many studies show that persons in lower socioeconomic positions, such as low-income groups, have higher risk of dying from stroke.⁽²⁸⁻²⁹⁾ Understanding the causal associations between SES and stroke will allow interventions to be appropriately targeted and assessed.

Even though age, decreased level of consciousness, ICU admission and hypertension were removed when entered in the multivariate Cox regression, they were positively associated with death at both 1-month and 1-year periods and with overall death in the univariate analysis. In fact, they emerged as predictors of stroke mortality in many previous studies.^(15-20,24)

Strengths and Limitations of the Study

This study has some limitations. The first limitation is the small number of patients. In fact,

Lebanon is a small country of approximately 4.3 million people in 2012.⁽³⁰⁾ Therefore, it was expected to have this number despite our effort to include all stroke patients in these 8 different hospitals in Beirut region. In addition, even though we have tried to screen all stroke patients in this study we might have missed some of them for different reasons (such as transferred patients to another hospital, etc...) which may also contribute to this small number of patient. However, we have no reason to believe that the associations we found would be different in larger more representative studies, except for some associations that may not show statistical significance because of the sample size of our study. Second, we did not include patients who died before hospitalization or died within less than 24 hour from admission which may give rise to a selection bias, and therefore we think that mortality rate is underestimated in our study. Third, even though patients came from all governorates, hospitals were limited to Beirut region. Future studies taking into account all the weak points and including a larger sample size from all Lebanon regions must be done to confirm our findings.

Conclusion

The important predictors of mortality found in our study were stroke severity and infectious complications. Low SES and the presence of comorbid conditions such as hypertension, atrial fibrillation and recurrent stroke were also predictors of long-term mortality.

There should be public awareness campaigns to educate the public on stroke symptoms and risk factors and their modifiable nature. Primary and secondary prevention measures should be of utmost importance. This will reduce both the prevalence of stroke and the severity and therefore the mortality rate.

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Conflicts of interest

All authors declare that they have no conflict of interest.

Table 1. Socio-demographic sample characteristics

	At enrolment		Survivors at 1-month follow up		Deceased at 1-month		P-value *	Survivors at 1-year follow up		Lost to follow up		P-value **	Deceased at 1-year		P-value***
	N=203		N=176		N=27			N=156		N=5			N=42		
	N./mean	%/SD	N./mean	%/SD	N./mean	%/SD		N./mean	%/SD	N./mean	%/SD		N./mean	%/SD	
Age mean	68.8	12.9	67.6	12.6	76.6	12.2	0.001	67.1	12.4	64.4	18.0	NS	75.8	12.0	<0.001
Gender							NS					NS			NS
Male	117	57.6	105	59.0	12	48.0		91	58.3	4	80.0		22	52.4	
Female	86	42.4	73	41.0	13	52.0		65	41.7	1	20.0		20	47.6	
Marital status							0.027					NS			NS
Single/															
Divorced/	81	39.9	66	37.1	15	60.0		58	37.2	2	40.0		21	50.0	
Widowed															
Married	122	60.1	112	62.9	10	40.0		98	62.8	3	60.0		21	50.0	
Employment status							0.044					NS			0.004
Employed	61	30.0	59	33.1	2	8.0		55	35.3	2	40.0		4	9.5	
Housewife	82	40.4	69	38.8	13	52.0		61	39.1	1	20.0		20	47.6	
Retired	21	10.3	18	10.1	3	12.0		16	10.3	1	20.0		4	9.5	
Unemployed	39	19.2	32	18.0	7	28.0		24	15.4	1	20.0		14	33.3	
Education							NS					NS			NS
Illiterate	37	18.2	33	18.5	4	16.0		30	19.2	0	0.0		7	16.7	
Elementary	86	42.4	73	41.0	13	52.0		60	38.5	3	60.0		23	54.8	
Secondary	35	17.2	32	18.0	3	12.0		29	18.6	1	20.0		5	11.9	
High school	27	13.3	24	13.5	3	12.0		23	14.7	1	20.0		3	7.1	
University	18	8.9	16	9.0	2	8.0		14	9.0	0	0.0		4	9.5	
Monthly personal income (US\$)							0.034					NS			0.012
<500	137	67.5	113	64.2	24	88.9		98	62.8	2	40.0		37	88.1	
[500-1000]	44	21.7	43	24.4	1	3.7		40	25.6	2	40.0		2	4.8	
[1000-1500]	11	5.4	9	5.1	2	7.4		8	5.1	1	20.0		2	4.8	
>1500	11	5.4	11	6.3	0	0.0		10	6.4	0	0.0		1	2.4	
Living status							NS					NS			NS
With family	178	87.7	160	89.9	19	76.0		139	89.1	5	100.0		35	83.3	
Alone	25	12.3	18	10.1	6	24.0		17	10.9	0	0.0		7	16.7	

* comparison patients with 1-month follow up (n=176) to dead at 1-month (n=27).

**comparison patients with full follow up (n=156) to lost to follow up (n=5).

*** comparison patients with full follow up (n=156) to dead (n=42).

Table 2. Clinical sample characteristics

	At enrolment		Survivors at 1-month follow up		Deceased at 1-month		P-value *	Survivors at 1-year follow up		Lost to follow up		P-value **	Deceased at 1-year		P-value** *
	N=203		N=176		N=27			N=156		N=5			N=42		
	N./mean	%/SD	N./mean	%/SD	N./mean	%/SD		N./mean	%/SD	N./mean	%/SD		N./mean	%/SD	
Type of stroke							NS					NS			NS
IS	161	79.3	139	79.0	22	81.5		123	78.8	3	60.0		35	83.3	
TIA	12	5.9	11	6.3	0	0.0		12	7.7	0	0.0		0	0.0	
PICH	14	6.9	14	8.0	3	11.1		10	6.4	0	0.0		4	9.5	
SAH	16	7.9	12	6.8	2	7.4		11	7.1	2	40.0		3	7.1	
Risk factors															
-Hypertension	153	75.7	130	73.9	24	88.9	NS	112	71.8	4	80.0	NS	38	90.5	0.012
-Dyslipidemia	76	37.6	68	38.6	9	33.3	NS	59	37.8	1	20.0	NS	17	40.5	NS
-DM	83	41.1	73	41.5	10	37.0	NS	63	40.4	2	40.0	NS	18	42.9	NS
-AF	26	12.9	25	14.2	2	7.4	NS	19	12.2	0	0.0	NS	8	19.0	NS
- CHD	54	26.6	49	27.8	5	18.5	NS	41	26.3	0	0.0	NS	13	31.0	NS
-Smoker							NS					NS			NS
▪ex-smoker	31	15.3	27	15.3	4	14.8		23	14.7	0	0.0		8	19.0	
▪current smoker	102	50.5	91	51.7	11	40.7		80	51.3	2	40.0		20	47.6	
First ever stroke/TIA	171	84.2	148	84.1	23	85.2	NS	134	85.9	4	80.0	NS	33	78.6	NS
NIHSS on admission							<0.001					NS			<0.001
0	13	6.4	13	7.4	0	0.0		13	8.3	0	0.0		0.0	0.0	
[1-4]	63	31.0	61	34.7	2	7.4		58	37.2	1	20.0		4	9.5	
[5-14]	67	33.0	63	35.8	4	14.8		57	36.5	2	40.0		8	19.0	
[15-20]	18	8.9	15	8.5	3	11.1		12	7.7	1	20.0		5	11.9	
≥21	42	20.7	24	13.6	18	66.7		16	10.3	1	20.0		25	59.5	
mRS at discharge					-	-	-					NS			<0.001
[0-2]	61	30.0	61	34.7				60	38.5	1	20.0		0	0.0	
[3-5]	115	56.5	115	65.3				96	61.5	4	80.0		15	35.7	
6	27	13.3						0	0.0	0	0.0		27	64.3	
BI at discharge					-	-	-					NS			<0.001
[96-100]	49	27.8	49	27.8				48	30.8	1	20.0		0.0	0.0	
[75-95]	32	18.2	32	18.2				32	20.5	0	0.0		0.0	0.0	
[46-74]	30	17.0	30	17.0				26	16.7	2	40.0		2	13.3	
[0-45]	65	36.9	65	36.9				50	32.1	2	40.0		13	86.7	

	At enrolment		Survivors at 1-month follow up		Deceased at 1-month		P-value *	Survivors at 1-year follow up		Lost to follow up		P-value **	Deceased at 1-year		P-value** *
	N=203		N=176		N=27			N=156		N=5			N=42		
	N./mean	%/SD	N./mean	%/SD	N./mean	%/SD		N./mean	%/SD	N./mean	%/SD		N./mean	%/SD	
TOAST							NS					NS			0.045
LA	37	21.4	31	20.5	6	27.3		28	20.7	0	0.0		9	25.7	
CE	55	31.8	46	30.5	9	40.9		38	28.1	1	33.3		16	45.7	
SV	27	15.6	26	17.2	1	4.5		26	19.3	1	33.3		1	2.9	
UC	54	31.2	48	31.8	6	27.3		43	31.9	1	33.3		9	25.7	
Bamford							NS					NS			0.020
LACS	27	16.8	26	18.7	1	4.5		26	21.1	1	33.3		1	2.9	
POCS	31	19.3	26	18.7	5	22.7		21	17.1	0	0.0		10	28.6	
TACS	5	3.1	3	2.2	2	9.1		2	1.6	0	0.0		3	8.6	
PACS	96	47.3	82	59.0	14	63.6		72	58.5	2	66.7		21	60.0	
POCS+PACS	2	1.2	2	1.4	0	0.0		2	1.6	0	0.0		0	0.0	
Surgery	26	13.1	23	13.1	5	18.5	NS	16	10.3	2	40.0	NS	10	23.8	0.021
Infectious complication	60	30.3	40	22.7	22	81.5	<0.001	29	18.6	2	40.0	NS	31	73.8	<0.001

IS=ischemic stroke; TIA=transit ischemic attack; PICH=primary intracerebral hemorrhage; SAH=subarachnoid hemorrhage; DM=diabetes mellitus; AF=atrial fibrillation; CHD=coronary heart disease; NIHSS= National Institution of Health Stroke Scale; mRS=modified Rankin Scale; BI=Barthel Index; TOAST=Trials of Org 10172 in Acute Stroke Treatment; LA=large-artery atherosclerosis; CE=cardioembolism; SV=small-vessel occlusion; UC=unclassified.

* comparison patients with 1-month follow up (n=176) to dead at 1-month (n=27).

**comparison patients with full follow up (n=156) to lost to follow up (n=5).

*** comparison patients with full follow up (n=156) to dead (n=42).

Table 3. Univariate Cox survival regression for determinants of 1-month, 1-year and overall mortality in stroke patients.

	1-month mortality				1-year mortality*				Overall mortality			
	B	HR	95% CI	P	B	HR	95% CI	P	B	HR	95% CI	P
Age												
≤64 years		1 (Ref.)								1 (Ref.)		
>64 years	0.9	2.5	[0.9-6.6]	0.065					0.8	2.2	[1.1-4.5]	0.039
Marital status												
Single/ Divorced/ Widowed		1 (Ref.)										
Married	-0.8	0.4	[0.2-0.9]	0.034								
Monthly personal income (US\$)	-0.7	0.5	[0.2-1.0]	0.050					-0.7	0.5	[0.3-0.9]	0.021
Living situation												
With family		1 (Ref.)										
Other	0.8	2.2	[0.9-5.4]	0.092								
Intensive care unit	2.5	12.5	[3.0-52.9]	<0.001					1.5	4.6	[2.1-9.9]	<0.001
Decreased level of consciousness	1.0	2.7	[1.7-4.3]	<0.001	1.1	3.0	[1.6-5.5]	<0.001	1.0	2.8	[1.9-4.1]	<0.001
Stroke severity on admission (NIHSS)	1.0	2.8	[1.9-4.2]	<0.001	0.8	2.3	[1.5-3.6]	<0.001	0.9	2.6	[1.9-3.5]	<0.001
Infectious complications	2.5	11.8	[4.5-31.2]	<0.001	1.8	5.8	[2.1-16.3]	0.001	2.2	8.7	[4.3-17.3]	<0.001
Surgery					1.4	3.9	[1.3-11.5]	0.012	0.8	2.2	[1.1-4.5]	0.030
Barthel Index at discharge	N/A				-1.6	0.2	[0.1-0.7]	0.008	N/A			
Modified Rankin Scale	N/A				1.5	4.7	[1.8-12.0]	0.001	N/A			
Recurrent stroke					1.0	2.8	[1.0-8.3]	0.057				
Hypertension	1.0	2.7	[0.8-8.9]	0.095	1.7	5.3	[0.7-40.2]	0.072	1.2	3.3	[1.2-9.3]	0.023
Atrial Fibrillation					1.4	4.2	[1.5-11.9]	0.006				
Employment status								0.053				0.011
Housewife						1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)
Employed					-1.0	0.4	[0.1-7.1]	0.236	-1.4	0.2	[0.1-0.7]	0.011
Retired					-0.8	0.6	[0.04-4.13]	0.680	-0.2	0.8	[0.3-2.3]	0.666
Unemployed					2.5	2.5	[2.7-51.8]	0.114	0.5	1.6	[0.8-3.2]	0.175

*Among 1-month survivors only.

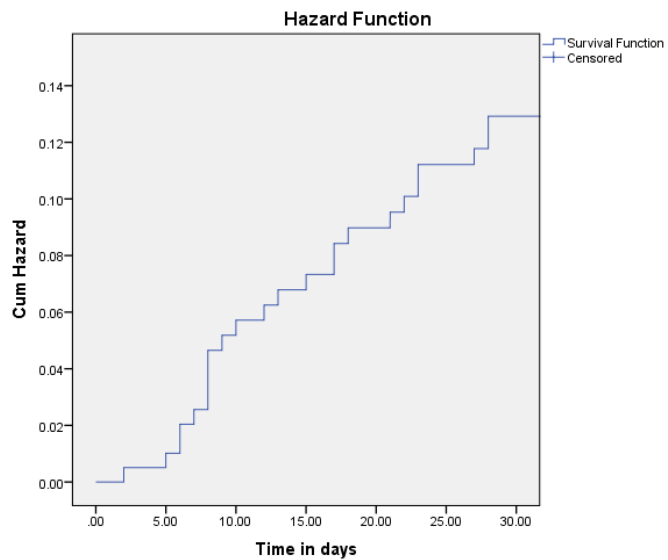


Fig. 1-A Kaplan-Meier mortality curve for stroke patients at 1-month follow-up.

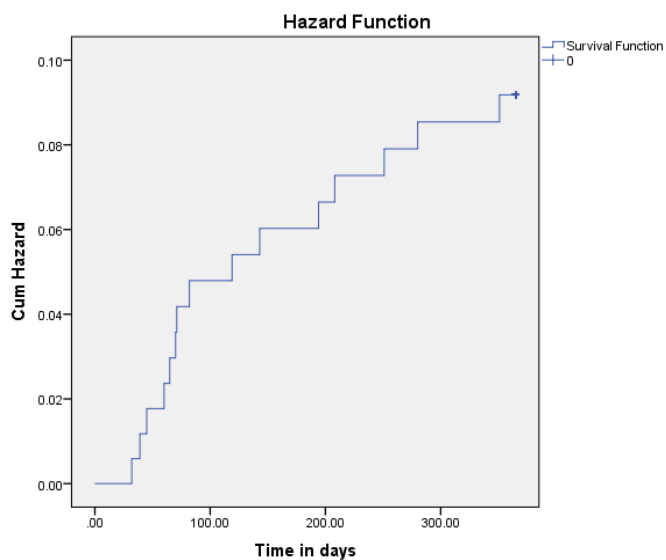


Fig. 1-B Kaplan-Meier mortality curve for stroke patients at 1-year follow-up (for 1-month survivors only).

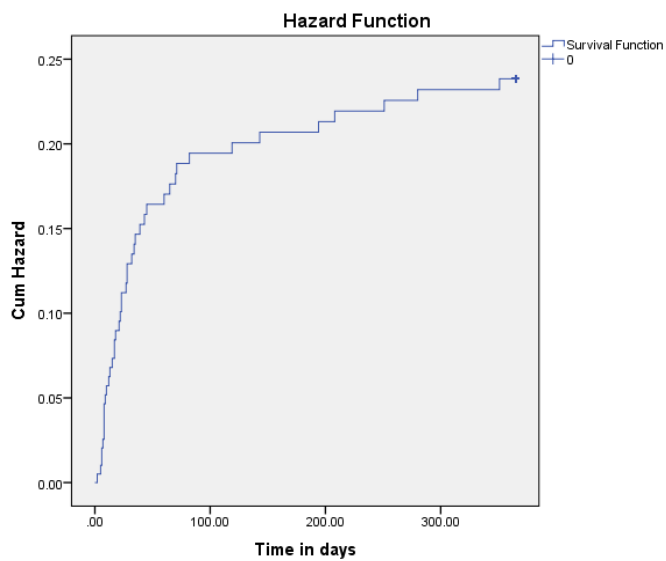


Fig. 1-C Kaplan-Meier mortality curve for stroke patients at 1-year follow-up (overall mortality).

Table 4. Multivariate Cox survival regression for determinants of 1-month, 1-year and overall mortality in stroke patients

	1-month mortality				1-year mortality*				Overall mortality			
	B	HR	95% CI	P	B	HR	95% CI	P	B	HR	95% CI	P
Stroke severity on admission (NIHSS)	0.7	2.0	[1.3-3.2]	0.003					0.7	2.0	[1.4-2.7]	<0.001
Infectious complications	1.4	4.2	[1.4-13.1]	0.013					1.4	4.1	[1.9-9.1]	<0.001
Barthel Index at discharge					-2.0	0.14	[0.04-0.50]	0.002				
Recurrent stroke					1.5	4.7	[1.2-17.7]	0.023				
Hypertension									1.0	2.7	[1.0-7.6]	0.059
Atrial Fibrillation					1.5	4.6	[1.1-19.2]	0.035				
Employment status				0.003				0.003				0.002
Housewife				1 (Ref.)				1 (Ref.)				1 (Ref.)
Employed				-2.5	0.8	[0.1-7.1]	0.828	-0.8	0.4	[0.1-1.3]	0.128	
Retired				-0.8	0.4	[0.04-4.13]	0.465	-0.3	0.7	[0.2-2.1]	0.569	
Unemployed				2.5	11.7	[2.7-51.8]	0.001	1.0	2.8	[1.4-5.7]	0.005	

*Among 1-month survivors only.

Reference

- 1- Feigin VL, Lawes CM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 2009 Apr; 8(4):355-69.
- 2- World Health Organization (WHO). Cardiovascular Diseases. Geneva, Switzerland: WHO; September 2009. WHO Fact Sheet 37.
- 3- Sagui E. *Med Trop (Mars).* 2007 Dec; 67(6):596-600.
- 4- MacKay J, Mensah GA. World Health Organization. Global Burden of Stroke. The Atlas of Heart Disease and Stroke. Available at: <http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf>. (Last accessed on 26 August 2018)
- 5- Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology.* 1999 Jul; 53(1):126-31.

- 6- Balami JS, Chen RL, Grunwald IQ, et al. Neurological complications of acute ischaemic stroke. *Lancet Neurol.* 2011 Apr; 10(4):357-71.
- 7- Riachy M, Sfeir F, Sleilaty G, et al. Prediction of the survival and functional ability of severe stroke patients after ICU therapeutic intervention. *BMC Neurology.* 2008; 8:24.
- 8- Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009; 40:2276.
- 9- The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke.* 1998; 28:2119–25.
- 10- Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; 337:1521–6.
- 11- Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke.* 1999 Aug; 30(8):1538-41.
- 12- Fattore G, Torbica A, Susi A, et al. The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC Neurol.* 2012; 12(1):137.
- 13- Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* 1993; 24(1):35-41.

- 14- Saposnik G, Hill MD, O'Donnell M, et al. Variables associated with 7-day, 30-day, and 1-year fatality after ischemic stroke. *Stroke* 2008; 39:2318–24.
- 15- Hartmann A, Rundek T, Mast H, et al. Mortality and causes of death after first ischemic stroke: the Northern Manhattan Stroke Study. *Neurology*. 2001 Dec 11; 57(11):2000-5.
- 16- Koton S, Tanne D, Green MS, et al. Mortality and predictors of death 1 month and 3 years after first-ever ischemic stroke: data from the first national acute stroke Israeli survey (NASIS 2004). *Neuroepidemiology*. 2010; 34(2):90-6.
- 17- Sawalha A.F. Characterization of Hospitalized Ischemic Stroke Patients in Palestine, *Libyan Journal of Medicine*. 2008; 4(1):37-40.
- 18- Al-Asadi JN, Habib HA. Risk factors and 30-day case fatality of first-ever stroke in Basrah, Iraq. *Nigerian Medical Journal : Journal of the Nigeria Medical Association*. 2014; 55(3):209-213.
- 19- Rønning OM. Very long-term mortality after ischemic stroke: predictors of cardiovascular death. *Acta Neurol Scand* 2013; 127(Suppl. 196):69–72.
- 20- Alonso A, Ebert AD, Kern R, et al. Outcome Predictors of Acute Stroke Patients in Need of Intensive Care Treatment. *Cerebrovasc Dis*. 2015; 40(1-2):10-7.
- 21- Ekeh B, Ogunniyi A, Isamade E, et al. Stroke mortality and its predictors in a Nigerian teaching hospital. *African Health Sciences*. 2015; 15(1):74-81.
- 22- Das S, Chandra Ghosh K, Malhotra M, et al. Short term mortality predictors in acute stroke. *Annals of Neurosciences*. 2012; 19(2):61-7.
- 23- Kaarisalo MM, Immonen-Räihä P, Marttila RJ, et al. Atrial fibrillation and stroke. Mortality and causes of death after the first acute ischemic stroke. *Stroke*. 1997 Feb; 28(2):311-5.

- 24- Sun, Y, Lee SH, Heng BH, et al. "5-year survival and rehospitalization due to stroke recurrence among patients with hemorrhagic or ischemic strokes in Singapore." *BMC Neurology* 2013; 13(1):133.
- 25- Carter AM, Catto AJ, Mansfield MW, et al. Predictive variables for mortality after acute ischemic stroke. *Stroke*. 2007 Jun; 38(6):1873-80.
- 26- European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; 25:457–507.
- 27- Higuchi S, Kabeya Y, Matsushita K, et al. Barthel Index as a Predictor of 1-Year Mortality in Very Elderly Patients Who Underwent Percutaneous Coronary Intervention for Acute Coronary Syndrome: Better Activities of Daily Living, Longer Life. *Clin Cardiol*. 2016 Feb; 39(2):83-9.
- 28- Cox AM, Mc Kevitt C, Rudd AG, et al. Socioeconomic status and stroke. *Lancet Neurol*. 2006 Feb; 5(2):181-8.
- 29- Ahacic K, Trygged S, Kåreholt I. "Income and Education as Predictors of Stroke Mortality after the Survival of a First Stroke," *Stroke Research and Treatment*, vol. 2012, Article ID 983145, 6 pages, 2012.
- 30- Bureau of Democracy, Human Rights, and Labor. "2012 Report on International Religious Freedom - Lebanon". 20 May 2013. Available at: <<https://www.state.gov/j/drl/rls/irf/2012/nea/208400.htm>> (Last accessed on 26 August 2018)

The high death proportions 1-month and 1-year post-stroke urge the need to implement serious measures to improve stroke care. Dependency in daily living activities was one of the long-term mortality predictors. Dependency in daily living activities leads to decline in HRQOL and depression, therefore we thought to assess HRQOL and depression 1-year post-stroke for stroke survivors and the factors affecting them.

Quality of life of 1-year stroke survivors and its predictors:
a multicenter prospective Lebanese cohort study

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Short title: Quality of life of 1-year survivors and its predictors in Lebanon

Abstract

Background: Stroke has a major impact on survivors including Health Related Quality Of life (HRQOL). It is crucial to identify factors influencing HRQOL in stroke survivors in this setting so that such factors can be efficiently manipulated in order to maximize HRQOL improvement. We sought to assess HRQOL 1-year post-stroke and the factors affecting it for patients with stroke.

Methods: This study was designed as a multicenter prospective cohort study in which 150 stroke patients were followed up at hospital discharge, at 3, 6, and 12 months post-stroke. HRQOL levels were determined at 1-year using both generic scale: the Short Form-36 (SF-36) survey and disease-specific scale: the stroke-specific quality of life (SS-QOL) scale. HRQOL determinants were sought among variables such as age, gender, socio-economic status, side, type and number of strokes, NIHSS, modified Rankin scale, BI, and depression (using the geriatric depression scale (GDS-15)).

Results: A total of 150 stroke patients were included. The mean SS-QOL was 3.7 ± 1.1 and that of SF-36 was 57.2 ± 25.5 . More than 15% of stroke patients were depressed. The main determinants of HRQOL were functional status, dependency in daily living activities, stroke severity, age and depression. The main determinants of depression were functional status and HRQOL (physical component of SF-36).

Conclusion: HRQOL of stroke patients is relatively low. The fact that the main determinant of HRQOL was functional status suggest that improving physical function may be helpful in providing a better HRQOL for stroke patients and therefore decrease the high depression rate.

Keywords: Quality of life; predictors; stroke; Lebanon; SF-36; SS-QOL

Introduction

Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity (WHO). Quality of life is a multi-dimensional construct that consists of at least three broad domains: physical, mental and social. Researchers and physicians have often used the health-related quality of life (HRQOL) concept in the field of medicine, which specifically focuses on the impact of an illness and/or the treatment on the patients' perception, of their status of health, and, on subjective well-being or satisfaction with life (Jaracz and Kozubsi, 2003). To assess HRQOL several instruments have been developed. Most of them are questionnaires based on a patient's subjective self-report or self-evaluation. The distinction is made between generic and specific measures. The latter involve items concerning a particular disease or health problem and are considered more sensitive than the generic ones, especially when detecting changes or differences among treatments (Opara and Jaracz, 2010). While the generic ones are used to evaluate quality of life for many types of diseases and for calculating utility values in cost-effectiveness analysis (Mehta et al., 2003).

Innovations and major improvements in acute stroke care have been raising post-stroke survival rates (van Eeden et al., 2015). Stroke is often catastrophic and affects all aspects of an individual's life, and unlike other disabling conditions the onset of stroke is sudden leaving the individual and family ill-prepared to deal with the sequelae (Mayo et al., 1999). Accordingly, more people experience long-term difficulties in terms of quality of life (Carod-Artal et al., 2000), social reintegration (Hommel et al., 2009), life satisfaction (Ostwald et al., 2009), and emotional functioning, including depression and anxiety (Bergersen et al., 2010).

HRQOL measurements are potentially more relevant to patients than measurements of impairments or disability and are an important index of outcome after stroke that can facilitate a broader description of disease and outcome (Abubakar and Isezuo, 2012). Quality of life related to stroke and life satisfaction after stroke is important health care issues that have not received sufficient attention in Lebanon.

It is crucial to identify factors influencing HRQOL in stroke survivors so that such factors can be efficiently manipulated in order to maximize HRQOL. Therefore, variables that predict HRQOL are of special interest. However, no study on HRQOL of Lebanese stroke patients exist to date. Therefore the aim of this study was to determine the HRQOL 1-year after stroke and to identify the factors related with and determinants of HRQOL in Lebanese stroke patients. The

results may provide valuable information about strategies that professionals and provider of stroke care can address to improve HRQOL.

Methods

Study design

This prospective study was conducted from 8 different hospitals in Beirut, over a period of 1-year after approval from the Institutional Ethics Committee. Participants (or their responsible caregivers where not possible) provided written informed consent.

All acute stroke patients over the age of 18 years admitted to each participating hospital from August 2015 with confirmed diagnosis of stroke (confirmed by a neurologist with radiological evidence by either CT scan and/or MRI) were recruited prospectively and followed up for 1-year or until death.

Stroke was defined according to the International Classification of Diseases (10th revision) and Transient Ischemic Attack (TIA) was defined as a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischemia and not associated with cerebral infarction (Easton et al., 2009).

Patients who did not want to be the part of the study (negative consent), or those who had a stroke of more than one week were excluded. Patients were also excluded if they were suffering from severe pathologies (cancer, fatal renal, hepatic or respiratory insufficiency), or having a moderate to severe cognitive decline before their stroke.

Study tools

National Institution of Health Stroke Scale (NIHSS) score was used to assess stroke impairment and severity (NINDS t-PA Stroke Study Group, 1998). Functional disability were assessed using the modified Rankin scale (mRS) and the Barthel Index (BI) (Sulter et al., 1999). Stroke etiology was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al., 1993).

HRQOL levels were determined at 1-year using both generic scale: the Short Form-36 (SF-36) survey and disease-specific scale: the stroke-specific quality of life (SS-QOL) scale. We used

the validated Arabic version of the SF-36 (Sabbah et al., 2003). Since no validated Arabic version of SS-QOL exists to date, the SS-QOL was translated in this procedure:

1- a forward translation of the original questionnaire (from English to Arabic language) by a qualified independent, native linguistic expert translator.

2- a back translation (from Arabic language to English) by another translator (blinded to the original English version).

3- the back translated questionnaire was discussed with the researchers R.A. and R.R. with both translators to come up with the final Arabic version of the SSQOL questionnaire.

4- The questionnaire was pre-tested on a convenient sample of 5 patients who already had a stroke episode and modified the very few questions that sounded unclear for them or misunderstood by them.

The validated Arabic version of the Geriatric Depression Scale (GDS) (Short Form 15-item) was used to assess depression (Chaaya et al., 2008).

Statistical analysis

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corporation, Armonk, NY, USA). Two researchers audited 5% randomly selected questionnaires. Data entry showed high reliability (error rate <1%). Data were presented as means±SDs or as percentages. In bivariate analyses, Pearson correlation coefficients were used for two continuous quantitative variables, Student's test for means comparison between two groups (for quantitative variables) and Chi-square test (or exact Fisher) for comparing percentages (for nominal, ordinal and categorical variables) were used. ANOVA (analysis of variance) test was used to compare between-group differences; followed by Bonferroni post-hoc when a significant difference was obtained. $P \leq 0.05$ indicated statistical significance. Bivariate analysis were done for the following dependent variables: SS-QOL, SF-36 and GDS-15. HRQOL and depression predictors were determined through multivariable stepwise linear regressions, after ensuring sample and conditions adequacy. HRQOL determinants were sought among variables such as age, gender, socio-economic status, side, type and number of strokes, NIHSS, modified Rankin scale, BI, and depression. Independent variables with $P < 0.2$ in the bivariate analysis were entered into the models. Regression was checked for collinearity (VIF < 10 indicated non-collinearity).

Results

Out of 203 recorded strokes, only 150 stroke patients were included in this study (dead =42; lost to follow up =11). The mean age of the study group was 67.3 ± 12.2 years and there were more males than females (57.3%). No significant difference was observed between lost to follow up and followed up patients concerning socio-demographic (**Table 1**).

HRQOL varied significantly between males and females in both SS-QOL and SF-36 where females tended to have low HRQOL than males ($P<0.001$). Older patients had significantly lower HRQOL ($P<0.001$). Patients with higher SES had better HRQOL scores in both specific ($P=0.075$) and generic ($P=0.036$) HRQOL scales. Patients with higher NIHSS and mRS had significantly lower HRQOL while patients with higher BI score had significantly higher HRQOL ($P<0.001$). Patients with TIA, SV and UC strokes had significantly higher HRQOL in both generic and specific scales ($P=0.012$ and 0.032 respectively). Patients with higher GDS-15 scores had significantly lower HRQOL ($P<0.001$ in both SS-QOL and SF-36). Patients with high HRQOL on SS-QOL had also high HRQOL on SF-36 (**Table 2**).

More than 15% of stroke patients were suffering from depression and more than 30% were suggested to be depressed. Females tended to be depressed more than males ($P=0.039$). However no significant difference was detected between age, SES, stroke type and depression. Patients with higher NIHSS and mRS had significantly more depressive symptoms while patients with higher BI score had significantly lower depressive symptoms ($P<0.001$). Patients with LA or CE stroke had significantly more depressive symptoms than those with SV or UC strokes ($P=0.003$). Depressed patients had significantly lower HRQOL ($P<0.001$ for both SS-QOL and SF-36) (**Table 3**).

Reliability (intra and inter), central tendency, and variability of the SS-QOL scale and the SF-36 scale in this stroke study were good. Stroke patients had relatively low HRQOL scores on both scales (3.7 ± 1.1 and 57.2 ± 25.5 respectively) (**Tables 4-5**).

Predictors of SS-QOL were mRS at 12 months, BI at 12 months and GDS-15 at 12 months. Predictors of SF-36 were age, SES (monthly home income), mRS at 12 months, BI at 12 months and GDS-15 at 12 months (**Table 6**). Predictors of GDS-15 were age, NIHSS at 12 months, BI at 12 months, type of stroke, and SF-36 (physical, general health and emotional components) (**Table 7**).

Discussion

This study pioneers in analyzing the HRQOL of stroke patients in Lebanon and evaluating its predictors. The mean of HRQOL in both SF-36 and SS-QOL was relatively low. Several studies have shown that by far the largest part of the patients experience and report a decline in HRQOL after stroke (Duncan et al., 1997; Hackett et al., 2000; Jonkman et al., 1998; Kwon et al., 2018; Williams et al., 1999), and this even applies to persons who have suffered only a minor stroke (Duncan et al., 1997; Williams et al., 1999). In fact, the health change item in the SF-36 had the lowest mean. There are a number of factors which seem to be contributing towards a decline in HRQOL of stroke patients.

In our study, age was negatively correlated to HRQOL (with SF-36 but not with SS-QOL); advanced age patients had a lower perceived HRQOL compared to younger patients. The effect of age on HRQOL in stroke survivors in the literature has remained inconclusive. Some studies showed that age had a strong influence on quality of life (Gurcay et al., 2009; Hackett et al., 2000; Kwon et al., 2018; Lai et al., 2002), while others found that there was no negative influence of age in patients with stroke (Gokkaya et al., 2005; Langton Hewer, 1990).

We found significant association between mRS (negative association), BI (positive association) and HRQOL (both SS-QOL and SF-36). The more patients had physical disability, the more they were dependent in activities of daily living, the more they had lower HRQOL scores. In fact, many authors have reported a strong association between physical disability, dependency in activities of daily living and HRQOL (Anderson et al., 1996; Duncan et al., 1997; Hackett et al., 2000; Jeon et al., 2017; King, 1996; Kwa et al., 1996; Lopez-Espuela et al., 2015; Owolabi, 2008; Williams et al., 1999). Moreover, stroke survivors, even if they are independent in their daily activities, have reported a decline in their HRQOL (Duncan et al., 1997). This seems to indicate that functional measurements only are not sufficient for determining stroke results. It is necessary too, in addition to the impartial assessment of physical impairments, to measure the HRQOL to provide a more accurate and complete picture of the post-stroke level of disability (Krančiukaite and Rastenyte, 2006).

Post-stroke depression is common (Whyte and Mulsant, 2002). More than 15% of stroke survivors had self-reported depressive mood in our study which was a bit lower than that reported in a previous Korean study (Kwon et al., 2018). From 23 to 41% of stroke patients feel an immediate inception of depression in the period of the few months after the stroke event

(Wilkinson et al., 1997). The existence of depression has a strong correlation with the prognosis of declined HRQOL after stroke (Jonkman et al., 1998; King, 1996; Neau et al., 1998; Williams et al., 1999). In several previous studies, post-stroke depression was associated with worse recovery and outcomes in multiple functional domains such as activity limitations and participation restrictions (Chau et al., 2009; Parikh et al., 1990; van de Weg et al., 1999), which leads to worse HRQOL in stroke survivors (Jeon et al., 2017; Rastenyte and Kranciukait, 2007). Therefore, comprehensive medical attention including treatment of depression should be provided in post-stroke rehabilitation, and depression screening and community-based interventions with support from other family members or caregivers has to be considered in chronic stroke survivors (Kwon et al., 2018).

SES was correlated to HRQOL, patients with higher monthly home income had higher HRQOL. Associations of SES with HRQOL have been previously reported in a number of chronic diseases (Mielck et al., 2014) including stroke (Baumann et al., 2014)

In the bivariate analysis, females had significantly lower HRQOL. However, gender and HRQOL disappeared in the multivariate analysis. The correlation between gender and QOL has remained obscure. C. S. Anderson *et al.* showed that women had a better stroke outcome in terms of social functioning and mental health (Anderson et al., 1996), but most authors report QOL either to be independent of gender (Kwa et al., 1996) or lower in females (Angeleri et al., 1996; Lopez-Espuela et al., 2015).

Stroke severity (NIHSS) and physical disability (SF-36 physical component) were consistently associated with depression. Our results were consistent with previous studies (Hackett and Anderson, 2005; Shi et al., 2017; Vojtkiv-Samoilovska and Arsovska, 2018). When we include the emotional and general health components of SF-36 in the depression model, they eliminate all other depression predictors. This means that emotional and general status components are intermediate factors between physical component and depression. Physical problems are leading to lower general health and emotional HRQOL and the latter are leading to depression.

Strengths and limitations of this study

To our knowledge, this is the first study assessing HRQOL and its determinants in Lebanese stroke patients. We used both generic and disease-specific scales for HRQOL and a validated geriatric depression scale (GDS-15) for depression. We did not exclude aphasic patients which is a limitation in many previous studies.

This study does, however, have limitations. The first limitation is the relatively small number of patients. Another limitation of this study is that it was conducted only in Beirut. Therefore, maybe some of our results are not generalizable to other regions of Lebanon. A third limitation is that when mute or global aphasic patients couldn't give clear answers, their caregivers responded. A larger multicenter study covering the whole geographic area of Lebanon is recommended.

Conclusion

The impact of stroke on HRQOL may be disastrous; stroke can affect multiple domains of life. More efforts and means should be applied to improving this facet of after stroke care such as helping patients with their reintegration in the community and the readjustment of their lives in order to reduce post-stroke depression rates. A long-term treatment goal in stroke survivors is to achieve HRQOL scores that are as high as possible.

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Conflicts of interest

All authors declare that they have no conflict of interest.

Table 1. Socio-demographic sample characteristics

	At enrolment		Survivors at 1-year follow up		Lost to follow up		P-value*	Deceased at 1-year		P-value**
	N=203		N=150		N=11			N=42		
	N/ mean	%/SD	N/ mean	%/SD	N/ mean	%/SD		N/ mean	%/SD	
Age	68.8	12.9	67.3	12.2	62.4	15.0	NS	75.8	12.0	<0.001
Gender							NS			NS
Male	117	57.6	86	57.3	9	81.8		22	52.4	
Female	86	42.4	64	42.7	2	18.2		20	47.6	
Marital status							NS			NS
Single/ Divorced/ Widowed	81	39.9	55	36.7	5	45.5		21	50.0	
Married	122	60.1	95	63.3	6	54.5		21	50.0	
Employment status							NS***			0.004
Employed	61	30.0	51	34.0	6	54.5		4	9.5	
Housewife	82	40.4	61	40.7	1	9.1		20	47.6	
Retired	21	10.3	16	10.7	1	9.1		4	9.5	
Unemployed	39	19.2	22	14.7	3	27.3		14	33.3	
Education							NS***			NS
Illiterate	37	18.2	28	18.7	2	18.2		7	16.7	
Elementary	86	42.4	59	39.3	4	36.4		23	54.8	
Secondary	35	17.2	28	18.7	2	18.2		5	11.9	
High school	27	13.3	23	15.3	1	9.1		3	7.1	
University	18	8.9	12	8.0	2	18.2		4	9.5	
Monthly home income (US\$)							NS***			NS
<500	60	29.6	40	26.7	3	27.3		17	40.5	
[500-1000]	62	30.5	50	33.3	3	27.3		9	21.4	
[1000-1500]	37	18.2	29	19.3	4	36.4		4	9.5	
>1500	44	21.7	31	20.7	1	9.1		12	28.6	
Living status							NS			NS
With family	178	87.7	136	90.7	8	72.7		35	83.3	
Alone	25	12.3	14	9.3	3	27.3		7	16.7	

*comparison patients with full follow up (n=150) to lost to follow up (n=11).

** comparison patients with full follow up (n=150) to dead (n=42).

***non parametric test.

Table 2. Bivariable analysis of HRQOL (SS-QOL and SF-36)

	Quality of Life			
	SS-QOL	P-value	SF-36	P-value
Gender				
Male	3.9±1.0	0.001	63.0±26.4	0.001
Female	3.3±1.0		49.7±22.3	
Age	-0.281	<0.001	-0.385	<0.001
SES (USD)		NS (0.075)		0.036
<500	3.5±1.1		51.9±25.3	
[500-1,000[3.5±1.1		55.0±26.0	
[1,000-1,500]	3.6±1.2		59.1±25.4	
>1,500	4.1±0.8		68.5±21.2	
NIHSS				
at admission	-0.642	<0.001	-0.611	<0.001
at 12 months	-0.757	<0.001	-0.673	<0.001
BI				
at discharge	0.668	<0.001	0.657	<0.001
at 12 months	0.852	<0.001	0.761	<0.001
mRS				
at discharge	-0.601	<0.001	-0.619	<0.001
- Independent	4.3±0.6	<0.001	75.9±14.6	<0.001
- Dependent	3.2±1.1		46.2±24.3	
at 12 months	-0.855	<0.001	-0.821	<0.001
- Independent	4.5±0.5	0.040	78.6±12.2	NS
- Dependent	4.2±0.6		72.7±17.5	
TOAST		<0.001 ^a		<0.001
LA	3.4±0.9		49.5±22.7	
CE	3.3±1.1		46.3±26.1	
SV	4.1±0.7		65.8±19.5	
UC	4.1±0.9		70.4±20.6	
Stroke type		0.012 ^b		0.032 ^b
IS	3.6±1.0		56.2±25.1	
PICH	3.1±1.4		47.6±35.3	
SAH	3.5±1.4		55.5±24.5	
TIA	4.5±0.4		76.7±8.7	
GDS-15 at 12 months	-0.705	<0.001	-0.741	<0.001
SF-36 at 12 months	0.921	<0.001	-	-

SS-QOL= Stroke Specific Quality of Life Scale; SF-36= Short Form-36; SES= socioeconomic status; NIHSS= National Institute of Health Stroke Scale; mRS= modified Rankin Scale; BI= Barthel Index; TOAST= Trial of Org 10172 in Acute Stroke Treatment; LA= large-artery atherosclerosis; CE= cardioembolism; SV= small-vessel occlusion; UC= unclassified; IS= Ischemic stroke; TIA= Transit Ischemic Attack; PICH= Primary Intracerebral hemorrhage; SAH= Subarachnoid hemorrhage; GDS-15= Geriatric Depression Scale (Short Form 15 items).

^a LA vs. UC and SV; CE vs. UC and SV

^b TIA vs. ICH and IS

Table 3. Bivariable analysis of depression (GDS)

	Geriatric Depression Scale (Short Form 15-item)				P-value
	Normal 62(41.3%)	Post-stroke depression suggestion 18(12.0%)	Suggestion of depression 47(31.3%)	Indicative of depression 23(15.3%)	
Gender					0.039
Male	43(50.0%)	9(10.5%)	20(23.3%)	14(16.3%)	
Female	19(29.7%)	9(14.1%)	26(41.3%)	9(14.1%)	
Age	65.7±13.6	65.9±13.8	69.0±10.0	68.4±11.5	NS
SES (USD)					NS*
<500	18(45.0%)	3(7.5%)	13(32.5%)	6(15.0%)	
[500-1,000[16(32.0%)	8(16.0%)	20(40.0%)	6(12.0%)	
[1,000-1,500]	12(41.4%)	3(10.3%)	8(27.6%)	6(20.7%)	
>1,500	16(51.6%)	4(12.9%)	6(19.4%)	5(16.1%)	
NIHSS					
at admission	4.5±5.3	6.8±5.0	10.8±8.5	14.2±10.5	<0.001 ^a
at 12 months	0.4±1.4	2.1±3.5	3.5±4.9	6.2±7.8	<0.001 ^a
BI					
BI at discharge	80.8±29.6	63.4±37.7	46.2±37.0	41.4±40.5	<0.001 ^b
BI at 12 months	94.4±12.0	81.7±30.1	67.8±36.4	56.4±41.1	<0.001 ^a
mRS					
at discharge	2.0±1.7	3.0±1.7	3.8±1.4	3.5±1.8	<0.001 ^b
- Independent	38(66.7%)	7(12.3%)	7(12.3%)	5(8.8%)	<0.001
- Dependent	24(25.8%)	11(11.8%)	40(43.0%)	18(19.4%)	<0.001
at 12 months	1.0±1.3	1.9±1.6	2.7±1.8	3.2±1.8	<0.001 ^b
- Independent	49(55.7%)	12(13.6%)	19(21.6%)	8(9.1%)	<0.001
- Dependent	13(21.0%)	6(9.7%)	28(45.2%)	15(24.2%)	<0.001
TOAST					0.003*
LA	54(41.9%)	16(12.4%)	42(32.6%)	17(13.2%)	
CE	7(25.0%)	4(14.3%)	13(46.4%)	4(14.3%)	
SV	8(21.6%)	4(10.8%)	19(51.4%)	6(16.2%)	
SV	14(60.9%)	2(8.7%)	4(17.4%)	3(13.0%)	
UC	25(61.0%)	6(14.6%)	6(14.6%)	4(9.8%)	
Stroke type					NS*
IS	45(38.5%)	15(12.8%)	40(34.2%)	17(14.5%)	
PICH	5(50.0%)	1(10.0%)	1(10.0%)	3(30.0%)	
SAH	3(27.3%)	1(9.1%)	4(36.4%)	3(27.3%)	
TIA	9(75.0%)	1(8.3%)	2(16.7%)	0(0%)	
SS-QOL at 12 months	4.4±0.6	3.8±0.8	3.1±0.9	2.5±0.9	<0.001
SF-36 at 12 months	76.6±13.8	63.7±20.7	43.7±21.4	30.9±17.5	<0.001

*non parametric test

SES= socioeconomic status; NIHSS= National Institution of Health Stroke Scale; mRS= modified Rankin Scale; BI= Barthel Index; TOAST= Trial of Org 10172 in Acute Stroke Treatment; LA= large-artery atherosclerosis; CE= cardioembolism; SV= small-vessel occlusion; UC= unclassified; IS= Ischemic stroke; TIA= Transit Ischemic Attack; PICH= Primary Intracerebral hemorrhage; SAH= Subarachnoid hemorrhage; SS-QOL= Stroke Specific Quality of Life Scale; SF-36= Short Form-36.

^a Normal vs. suggestion of depression and indicative of depression and post-stroke depression suggestion vs. indicative of depression

^b Normal vs. suggestion of depression and indicative of depression

Table 4. Reliability, central tendency, and variability of the SS-QOL scale in this stroke study.

SS-QOL			
Scale	Mean±SD	Alpha	Items
Energy	3.0±1.4	0.914	3
Family roles	3.3±1.6	0.867	3
Language	4.4±1.3	0.985	5
Mobility	3.5±1.5	0.949	6
Mood	4.1±1.0	0.766	5
Personality	3.1±1.3	0.730	3
Self care	3.7±1.6	0.969	5
Social roles	3.0±1.4	0.870	5
Thinking	3.9±1.2	0.778	3
Upper extremity function	3.9±1.6	0.964	5
Vision	4.6±0.8	0.738	3
Work/productivity	3.0±1.7	0.979	3
Total	3.7±1.1	0.925	49

Table 5. Reliability, central tendency, and variability of the SF-36 scale in this stroke study.

SF-36			
Scale	Mean±SD	Alpha	Items
Physical functioning	53.7±34.4	0.933	10
Role functioning physical	49.0±48.1	0.972	4
Role functioning emotional	71.8±44.3	0.981	3
Energy/fatigue	55.0±22.3	0.862	4
Emotional well-being	60.0±21.9	0.860	5
Social functioning	60.3±37.3	0.863	2
Pain	78.1±25.8	0.864	2
General health	57.0±22.7	0.830	5
Health change	30.5±32.0	-	1
Total	57.2±25.5	0.898	36

Table 6. Multivariable linear regression analysis of HRQOL (SS-QOL and SF-36) predictors.

	SS-QOL ^a					SF-36 ^b				
Variables explained	86.9% of the variance of SS-QOL					82.7% of the variance of SF-36				
Anova	<0.001					<0.001				
Independent variables	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF
	B	SD				B	SD			
(Constant)	3.526					85.933				
Age						-0.248	0.075	-0.120	0.001	1.1
mRS at 12 months	-0.211	0.033	-0.357	<0.001	3.5	-6.014	0.903	-0.430	<0.001	3.6
BI at 12 months	0.013	0.002	0.391	<0.001	3.4	0.113	0.050	0.145	0.024	3.4
GDS-15 at 12 months	-0.087	0.009	-0.331	<0.001	1.4	-2.626	0.249	-0.424	<0.001	1.4
Monthly home income ≤ 1000 USD (ref.) > 1000 USD						3.598	1.790	0.070	0.046	1.0

mRS= modified Rankin Scale; BI= Barthel Index; SF-36= Short Form-36; SS-QOL= Stroke Specific Quality of Life Scale; GDS-15= Geriatric Depression Scale (Short Form15 items)

^a Dependent variable: SS-QOL at 12 months

Independent variables: sex, age, monthly home income, type of stroke (TIA vs. other), NIHSS at 12 months, mRS at 12 months, BI at 12 months and GDS-15 at 12 months.

^b Dependent variable: SF-36 at 12 months

Independent variables: sex, age, monthly home income, type of stroke (TIA vs. other), NIHSS at 12 months, mRS at 12 months, BI at 12 months and GDS-15 at 12 months.

Table 7. Multivariable linear regression analysis of depression (GDS-15) predictors

	GDS-15 ^a					GDS-15 ^b				
Variables explained	34.5% of the variance of GDS-15					59.0% of the variance of GDS-15				
Anova	<0.001					<0.001				
Independent variables	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF
	B	SD				B	SD			
(Constant)	8.663					14.122				
NIHSS at 12 months	0.145	0.071	0.170	0.047	1.6					
SF-36 physical component at 12 months	-0.044	0.011	-0.330	<0.001	2.0					
SF-36 general health component at 12 months						-0.052	0.014	-0.236	<0.001	1.4
SF-36 emotional at 12 months						-0.096	0.010	-0.619	<0.001	1.4

NIHSS= National Institution of Health Stroke Scale; SF-36= Short Form-36; Scale; GDS-15= Geriatric Depression Scale (Short Form15 items)

^a Dependent variable: GDS-15 at 12 months

Independent variables: sex, age, monthly home income, type of stroke (TIA vs. other), NIHSS at 12 months, mRS at 12 months, BI at 12 months and SF-36 at 12 months (physical component only; emotional and general health components were excluded). (SS-QOL at 12 months was removed from the model due to its high collinearity (VIF=10)).

^b Dependent variable: GDS-15 at 12 months

Independent variables: sex, age, monthly home income, type of stroke (TIA vs. other), NIHSS at 12 months, mRS at 12 months, BI at 12 months and SF-36 at 12 months (physical, general health and emotional components). (SS-QOL at 12 months was removed from the model due to its high collinearity (VIF=10)).

References

Abubakar SA, Isezuo SA. Health Related Quality of Life of Stroke Survivors: Experience of a Stroke Unit. *International Journal of Biomedical Science : IJBS*. 2012;8(3):183-187.

Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.

Anderson C, Laubscher S, Burns R. Validation of the shortterm 36 (SF-36) health survey questionnaire among stroke patients. *Stroke* 1996;27:1812-6.

Angeleri F, Angeleri VA, Foschi N, et al. The influence of depression, social activity, and family stress on functional outcome after stroke. *Stroke* 1993;24:1478-83.

Baumann M, Le Bihan E, Chau K, et al. Associations between quality of life and socioeconomic factors, functional impairments and dissatisfaction with received information and home-care services among survivors living at home two years after stroke onset. *BMC Neurol*. 2014 Apr 28;14:92.

Bergersen H, Frøslie KF, Stibrant Sunnerhagen K, et al. Anxiety, depression, and psychological well-being 2 to 5 years poststroke. *J Stroke Cerebrovasc Dis* 2010;19:364–9.

Carod-Artal J, Egido JA, Gonzalez JL, et al. Quality of life among stroke survivors evaluated 1 year after stroke: experience of a stroke unit. *Stroke* 2000;31:2995–3000.

Chaaya M, Sibai AM, Roueiheb ZE, et al. Validation of the Arabic version of the short Geriatric Depression Scale (GDS-15). *Int Psychogeriatr*. 2008 Jun;20(3):571-81.

Chau JP, Thompson DR, Twinn S, et al. Determinants of participation restriction among community dwelling stroke survivors: a path analysis. *BMC Neurol*. 2009 Sep 7; 9:49.

Duncan PW, Samsa GP, Weinberger M, al. Health status of individuals with mild stroke. *Stroke* 1997;28:740-5.

Easton JD, Saver JL, Albers GW, et al. American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009 Jun;40(6):2276-93.

Gokkaya NK, Aras MD, Cakci A. Health-related quality of life of Turkish stroke survivors. *Int J Rehabil Res*. 2005;28:229–235.

- Gurcay E, Bal A, Cakci A. Health-related quality of life in first-ever stroke patients. *Ann Saudi Med.* 2009;29:36–40.
- Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke.* 2005 Oct;36(10):2296-301.
- Hackett ML, Duncan JR, Anderson CS, et al. Health-related quality of life among long-term survivors of stroke: results from the Auckland Stroke Study. *Stroke* 2000; 31:440-7.
- Hommel M, Trabucco-Miguel S, Joray S, et al. Social dysfunctioning after mild to moderate first-ever stroke at vocational age. *J Neurol Neurosurg Psychiatry* 2009;80:371–5.
- Jaracz K, Kozubski W. Quality of life in stroke patients. *Acta Neurol Scand.* 2003 May; 107(5):324-9.
- Jeon NE, Kwon KM, Kim YH, Lee JS. The Factors Associated With Health-Related Quality of Life in Stroke Survivors Age 40 and Older. *Annals of Rehabilitation Medicine.* 2017;41(5):743-752.
- Jonkman EJ, de Weerd AW, Vrijens NLH. Quality of life after a first ischemic stroke. *Acta Neurologica Scandinavia* 1998;98: 169-75.
- King R. Quality of life after stroke. *Stroke* 1996;27:1467-72.
- Kranciukaite D, Rastenyte D. Measurement of quality of life in stroke patients. *Medicina (Kaunas).* 2006;42(9):709-16. Review.
- Kwa VI, Limburg M, de Haan RJ. The role of cognitive impairment in the quality of life after ischemic stroke. *J Neurol* 1996;243:599-604.
- Kwon S, Park JH, Kim WS, et al. Health-related quality of life and related factors in stroke survivors: Data from Korea National Health and Nutrition Examination Survey (KNHANES) 2008 to 2014. *PLoS One.* 2018 Apr10;13(4):e0195713.
- Lai SM, Studenski S, Duncan PW, et al. Persisting consequences of stroke measured by the stroke impact scale. *Stroke.* 2002;33:1840–1844.
- Langton Hewer R. Rehabilitation After Stroke. *Q J Med New Ser.* 1990;76:659–674.
- Lopez-Espuela F, Zamorano JD, Ramirez-Moreno JM, et al. Determinants of Quality of Life in Stroke Survivors After 6 Months, from a Comprehensive Stroke Unit: A Longitudinal Study. *Biol Res Nurs.* 2015 Oct;17(5):461-8.
- Mayo NE, Wood-Dauphinee S, Ahmed S, et al. Disablement following stroke. *Disabil Rehabil.* 1999 May-Jun; 21(5-6):258-68.
- Mehta T, Venkata Subramaniam A, Chetter I, et al. Disease-specific quality of life assessment in intermittent claudication (review) . *Eur J Vasc Endovasc Surg.* 2003; 25: 202–208

Mielck A, Vogelmann M, Leidl R. Health-related quality of life and socioeconomic status: inequalities among adults with a chronic disease. *Health Qual Life Outcomes*. 2014 Apr 25;12:58.

Neau JP, Ingrand P, Mouille-Brachet C, et al. Functional recovery and social outcome after cerebral infarction in young adults. *Cereb Dis* 1998;8:296-302.

Opara J, Jaracz K. Quality of life of post-stroke patients and their caregivers. *Journal of Medicine and Life*. 2010;3(3):216-220.

Ostwald SK, Godwin KM, Cron SG. Predictors of life satisfaction in stroke survivors and spousal caregivers after inpatient rehabilitation. *Rehabil Nurs* 2009;34:160–7, 174; discussion 174.

Owolabi MO. Determinants of health-related quality of life in Nigerian stroke survivors. *Trans R Soc Trop Med Hyg*. 2008 Dec;102(12):1219-25.

Parikh RM, Robinson RG, Lipsey JR, et al. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. *Arch Neurol*. 1990 Jul; 47(7):785-9.

Rastenyte D, Kranciukaite D. Poststroke depression and its impact on quality of life. *Medicina (Kaunas)*. 2007; 43(1):1-9.

Sabbah I, Drouby N, Sabbah S, et al. Quality of life in rural and urban populations in Lebanon using SF 36 Health Survey. *Health and Quality of Life Outcomes* 2003; 1:30.

Shi Y, Yang D, Zeng Y, Wu W. Risk Factors for Post-stroke Depression: A Meta-analysis. *Frontiers in Aging Neuroscience*. 2017;9:218.

Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke*. 1999;30(8):1538-41.

The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1998;28:2119–2125.

van de Weg FB, Kuik DJ, Lankhorst GJ. Post-stroke depression and functional outcome: a cohort study investigating the influence of depression on functional recovery from stroke. *Clin Rehabil*. 1999;13: 268–272.

van Eeden M, van Heugten C, van Mastrigt GAPG, et al. The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke. *BMJ Open* 2015;5:e008220.

Vojtkiv-Samoilovska D, Arsovska A. Prevalence and Predictors of Depression after Stroke - Results from a Prospective Study. *Open Access Macedonian Journal of Medical Sciences*. 2018;6(5):824-828.

Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biol Psychiatry*. 2002 Aug 1; 52(3):253-64.

Wilkinson PR, Wolfe CD, Warburton FG, et al. A long-term follow-up of stroke patients. *Stroke* 1997;28:507-12.

Williams LS, Weinberger M, Harris LE, et al. Measuring quality of life in a way that is meaningful to stroke patients. *Neurology* 1999;53:1839-43.

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Physical functional status is the main important predictor of HRQOL. However emotional status affects HRQOL too. DALYs represent the burden of the disease for humans. Despite the relatively high stroke prevalence and burden in Lebanon, its cost is not known. Therefore, the fourth study was designed to quantify the burden of stroke by providing detailed financial data on the direct in-hospital cost of acute stroke care in Lebanon and evaluate its drivers.

Direct medical cost of hospitalization for acute stroke in Lebanon: a prospective incidence-based multicenter cost-of-illness study

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Short title: Direct medical cost of hospitalization for acute stroke in Lebanon

Abstract

Background and Aims: Stroke is a major social and health problem posing heavy burden on national economies. We provided detailed financial data on the direct in-hospital cost of acute stroke care in Lebanon and evaluated its drivers.

Methods: This was an observational, quantitative, prospective, multicenter, incidence-based, bottom-up cost-of-illness study. Medical and billing records of stroke patients admitted to eight hospitals in Beirut over one year were analyzed. Direct medical costs were calculated and cost drivers were assessed using a multivariable linear regression analysis.

Results: In total, 203 stroke patients were included (male: 58%; mean age: 68.8±12.9 years). The direct in-hospital cost for all cases was US\$1,413,069 for 2626 days (US\$538 per in-hospital day). The average in-hospital cost per stroke patient was US\$6961±15,663. Hemorrhagic strokes were the most costly, transient ischemic attack being the least costly. Cost drivers were hospital length of stay, intensive care unit length of stay, type of stroke, stroke severity, modified Rankin Scale, third party payer, surgery and infectious complications.

Conclusion: Direct medical cost of acute stroke care represents high financial burden to Lebanese health system. Development of targeted public health policies and primary prevention activities need to take priority to minimize stroke admission in future and to contain this cost.

Keywords

Cost of Illness, Hospital Costs, Stroke, Lebanon, Prospective Studies, Health Policy, Incidence, Regression Analysis, Humans.

Introduction

Stroke is the second most frequent cause of death^{1,2} and the major cause of disability^{2,3} worldwide. Being a disease with long-term consequences, stroke creates considerable social and economic burden to individuals and society,³ resulting from its high prevalence, hospitalization rates, morbidity and mortality.⁴ Worldwide, stroke consumes about 2–4% of total healthcare costs.² In the US, total annual costs of stroke are expected to increase by 129%, reaching US\$240.67 billion by 2030.⁵ Taken the scarcity of healthcare resources, cost-of-illness (COI) studies in stroke care are needed to provide insights into the distribution of the cost and its impact on the national healthcare expenditure.⁶

Since investigations into economic impact of stroke are lacking in Lebanon, this study aimed to estimate cost of medical care during hospital admission, and to identify important variables that influence the cost in Beirut hospitals.

Methods

This study received ethical approval from the Institutional Review Board of each participating hospital. Signed informed consent was obtained from each patient or his caregiver after explaining the purpose and methods of the study.

Study Design

This is an observational, prospective, incidence-based, multicentre, COI study. Adult patients (≥ 18 years), diagnosed with acute stroke or Transient Ischemic Attack (TIA) (primary or recurrent) supported by computed tomography scan (CT scan) and/or magnetic resonance imaging (MRI) were included in this study between August 2015 and August 2016 from 8 hospitals in Beirut of whom 6 private university hospitals, 1 private community hospital and 1 public university hospital.

Stroke was defined according to the International Classification of Diseases (10th revision) including subarachnoid hemorrhage (SAH), primary intracerebral hemorrhage (PICH) and cerebral infarction. TIA was defined as a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischemia and not associated with cerebral infarction.⁷

Patients admitted after seven days of symptoms onset or those who have difficulty accepting follow-up visits were excluded. Patients were also excluded if they were: already dependent regarding activities of daily living (Barthel Index (BI) score ≤ 85); suffering from severe pathologies with unfavorable 1-year prognosis; disabling and progressive neurological diseases; cognitive decline (score >1 on Heteroanamnesis list Cognition)⁸ before their stroke.

Data Collection

Patients demographic (sex, age), socioeconomic profile (housing situation, socioeconomic status, employment status, third party payer (TPP), education level), risk factors, medical history including medical treatments, laboratory and imaging data, complications and rehabilitation therapy (physiotherapy and speech therapy) were collected at baseline and/or during hospitalization period. Current smokers were defined as persons who reported smoking at least 100 cigarettes during their lifetime and who, at the time they participated in the study, reported smoking every day or some days. Former smokers were defined as those who have smoked at least 100 cigarettes in their lifetime but who have quit smoking since a minimum of 28 days. A researcher pharmacist did the data collection.

Billing data were collected using a bottom-up approach. Costs of hospitalization of patients admitted to another hospital before being transferred to a participating hospital were also included. Costs were calculated according to the quantity of resources consumed by each patient from admission till discharge from hospital. The total direct medical cost per patient for each resource item was calculated as follows: total direct cost = \sum unit cost \times resource use. The bills for each patient were provided by the hospitals' administration including information related to cost of hospitalization, laboratory, radiology and cardiology-related investigations, medication,

nursing charges, physicians fees, and rehabilitation services. Costs calculated in Lebanese Pound (LBP) were converted to US\$ (exchange rate: US\$1=LBP 1508).⁹

Study tools

Pre-stroke functional disability was defined according to BI at admission, while functional disability at discharge were assessed using modified Rankin scale (mRS) and BI. Patients were divided into 3 groups according to their mRS score: independence (mRS 0–2), dependence (mRS 3–5) and death (mRS=6) and into four groups according to their BI: independence (96-100), mild dependence (75-95), moderate dependence (46-74) and severe dependence (0-45).^{3,4,10}

National Institution of Health Stroke Scale (NIHSS) score was used to classify stroke severity at admission into five categories (0=no stroke symptoms, 1-4=minor stroke, 5-14=moderate stroke, 15-20=moderate/severe, and 21-42=severe stroke).¹¹

Patients were classified into five etiologic/pathophysiological categories according to the Trial of Org 10172 in Acute *Stroke* Treatment (TOAST system)¹² and into 4 different stroke locations (lacunar stroke syndrome (LACS), partial anterior circulation stroke (PACS), posterior circulation stroke (POCS) and total anterior circulation stroke (TACS)) according to Bamford Scale (BS).¹³ Patients' assessment for the mRS, BI, NIHSS, and stroke diagnosis, classification and locations were performed by neurologists or neurologist resident.

Statistical analysis

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corporation, Armonk, NY, USA). Cost data entry was doubled checked. Two researchers audited 5% randomly selected questionnaires. Data entry showed high reliability (error rate <1%). Data were presented as means±SDs, except financial data presented also as medians and ranges. In bivariate analyses, Pearson correlation coefficients (or Spearman) were used for two continuous quantitative variables, Student's test (or Mann-Whitney) for means comparison between two groups (for quantitative variables) and Chi-square

test (or exact Fisher) for comparing percentages (for nominal, ordinal and categorical variables) were used. ANOVA (analysis of variance) test (or Kruskal Wallis) was used to compare between-group differences; followed by Bonferroni post-hoc when a significant difference was obtained. $P \leq 0.05$ indicated statistical significance. Bivariate analysis were done for the following dependent variables: LOS, ICU LOS and Cost.

Predictors of total hospital cost (all stroke type and IS only) and LOS were determined through multivariable stepwise linear regressions controlling for potential confounders, after ensuring sample and conditions adequacy. Logistic transformation $\ln(\text{cost of stroke})$ and $\ln(\text{length of stay (LOS)})$ were performed as their distributions were skewed. Transformed data were normally distributed, and were entered in each model as dependent variable. Independent variables with $P < 0.2$ in the bivariate analysis were entered into the models. Regression was checked for collinearity ($VIF < 10$ indicated non-collinearity). Confounders (age and sex) were entered to the model as independent variables.

Results

Demographic and clinical characteristics (Tables 1-2)

In this study, 203 patients were enrolled (mean age: 69 ± 13 years, men: 58%) (Table 1). Approximately 5% of eligible patients did not give their written consent and were therefore excluded from the study. The mean LOS was 13 ± 18 days. More than 50% were admitted to an intensive care unit (ICU) with a mean LOS of 6 ± 13 days (Table 2).

The mean NIHSS at admission was 11 ± 10 and 30% of the patients had an $\text{NIHSS} \geq 15$. Around 79% had an IS (22% due to large-artery atherosclerosis (LA), 33% cardio-embolism (CE), 17% small-vessel occlusion (SV) and 28% unclassified (UC)), 6.9% had a PICH, 7.9% had a SAH and 5.9% had a TIA. According to Bamford classification, the major affected territory was PACS (60%) (Table 2).

The mean mRS and BI scores at discharge were 3.5 ± 2.0 and 58.6 ± 38.8 , respectively and 30.0% of patients were independent at discharge (Table 2).

Patients with hemorrhage had more severe neurological deficits on admission, stayed longer in-hospital, required more ICU admissions, and had higher mortality rate; the survivors had worse functional outcome at discharge (Table 2).

Direct cost of stroke (Figure 1)

The direct in-hospital cost for all cases was US\$1,413,069 for a total stay of 2626 days (US\$538 per in-hospital day). The average cost per stroke patient was US\$6961 \pm 15,663. Of the total cost, 26.8% was attributed to the cost of room and board, 22.3% to general exams (including stroke and vascular imaging and cardiology-related investigations), 15.7% to physicians' fees, 14.4% to laboratory tests, 14.6% to pharmacy, and 6.2% to other expenses.

Predictors of cost (Tables 3-4)

Regarding stroke types, PICH were the most expensive (US\$26,698 \pm 50,400) followed by SAH (US\$21,257 \pm 14,625), which were significantly more expensive than IS (US\$4248 \pm 4352) and TIA (US\$1277 \pm 492) (Table 3).

Among ischemic stroke subtypes, the mean total cost was significantly higher for CE (US\$6064 \pm 5865) compared with SV and UC (US\$1827 \pm 1092, $P<0.001$; US\$3003 \pm 3251, $P=0.003$), respectively. According to Bamford classification, LACS had a significantly lower cost than POCS, TACS, PACS ($P=0.008$, 0.008 , <0.001 respectively) (Table 3).

Patients with infectious complications (i.e. pneumonia, urinary tract infection), or who underwent surgical intervention (i.e. coiling, shunt, craniotomy, endarterectomy, gastrostomy, tracheotomy) had a higher cost ($P<0.001$ for both) (Table 3).

LOS and total cost positively correlated with stroke severity. Patients who survived a severe stroke stayed in-hospital longer and had higher costs compared with those with less severe strokes ($P<0.001$ in both comparisons). The higher cost of severe strokes was also associated

with greater ICU use. Deceased patients used significantly more resources than survivors (US\$17,237±36,370 vs. US\$9166±11,388; $P<0.001$) (Table 3).

Total hospital costs strongly correlated with LOS ($r=0.835$, $P<0.001$), and ICU LOS ($r=0.794$, $P<0.001$), and moderately with admission NIHSS, mRS and BI discharge scores ($r=0.657$, $r=0.657$, $r=-0.634$ respectively, $P<0.001$). Total hospital costs did not significantly correlate with age ($r=0.052$, $P=0.459$), unless when SAH patients were excluded ($r=0.227$, $P=0.002$) (Table 3).

Total cost varied by discharge destination; those discharged to rehabilitation centers or nursing homes had a considerably higher cost than home and home with help ($P<0.001$) (Table 3).

Hospital LOS, ICU LOS, private TPP, hemorrhagic stroke, increased stroke severity on admission, having a surgery, infectious complication occurrence and high mRS score at discharge were independent predictors of increased total cost after accounting for confounding factors. ICU LOS accounted for 57% of the variance in total cost. Hospital LOS, ICU LOS and private TPP independently correlated with higher cost in ischemic strokes. In addition, LA and CE strokes, compared with SV and UC, and low BI at discharge were predictors of increased total cost (Table 4).

Predictors of LOS

Predictors of higher LOS were high NIHSS at admission, high mRS score at discharge, ICU LOS, having a surgery, infectious complication, discharge destination to a rehabilitation center or nursing home or death and female gender (Table 4).

Discussion

To the best of our knowledge, this is the first COI study analyzing the direct cost of in-patient medical care due to stroke in Lebanon and evaluating its drivers. The average in-hospital cost per stroke patient was US\$6961±15,663. Cost drivers were LOS, stroke types, severity, etiology, complications, dependency level and TPP.

Although a direct comparison is not possible, mean hospital cost per patient (US\$6961±15,663) was close to that reported from high-income countries (Greece US\$7130)¹⁴ or lower (USA US\$9688),¹⁵ yet it was higher than figures reported from middle and low-income countries (Turkey US\$1917,⁴ Pakistan US\$1578,¹⁶ Brazil US\$4687 for PICH and US\$2174 for IS,¹⁷ Argentina US\$14904 for PICH and US\$4717 for IS¹⁸) (all costs were adjusted to 2015 US\$ by purchasing power parities and consumer prices index).

The mean LOS for patients in this study was close to similar studies done in Turkey, Greece and Sweden,^{4,14,19} but considerably shorter than that reported in several high-income countries,^{20,21} though Spanish and US centers have reported shorter LOS.^{22,23,24}

As in other studies,^{16,22,25} hospital LOS accounted for a large proportion of the variance of total cost than other variables entered to the regression model. The costs for bed and staff accounted for more than a quarter of total cost. Thus, as it was expected, LOS was highly correlated, in a direct and linear relationship, with total cost. Our study confirms that cost of in-patient care is largely driven by LOS^{14,21}; decreasing the LOS might reduce in-hospital costs.²⁶ Investigating interventions aiming at decreasing LOS from the societal perspective on the long run are necessary to ensure that they do not simply result in shifting of costs to follow-up care, resulting from poor quality of care, more complications, or more frequent readmissions.

Of interest, cost for beds and staffs was lower than in high and middle-income countries.^{4,17,20,22} This might be partly due to the considerably shorter hospitalization in our study. In contrast, the cost for imaging and laboratory was similar or higher than in high and middle-income countries.^{4,20,22}

In this study, 53% of the patients were initially admitted to ICU with a mean LOS of six days. These figures are close to those from Japan²⁰ and a bit lower than Argentina and Brazil.^{17,18} Admission criteria to ICU were not clearly predefined and depended on physicians in charge and hospitals policy; patients with severely reduced level of consciousness, those who required continuous cardiac monitoring, and those with massive infarction were usually admitted.

Further studies are needed to elucidate the role of the stroke unit in acute stroke as a cost-effective model of care among stroke patients in Lebanon and advocate its implementation if found to be cost-effective.²⁷ In fact, stroke service may result in reduced LOS, and thus drive costs down.

We showed marked differences in in-patient costs, mortality and LOS according to different stroke types. Patients with PICH incurred the greatest cost, averaging US\$26,700; the median cost of PICH was 3 times higher than that of IS. Patients with a TIA were the least costly, averaging US\$1300. Furthermore, mortality and LOS were significantly higher in patients with PICH and SAH than those with ischemic stroke and TIA. As found in other high and middle-income countries,^{18,19,23,28-30} patients with PICH or SAH bore higher costs, mortality and LOS. Mean cost per discharge for PICH was higher than that in high-income countries,^{23,28,30} however costs of patients with SAH, TIA and IS were lower than those in high-income countries.^{22,23,28,30} In opposition to USA studies,^{23,28} mean cost of PICH was higher than SAH, however, the median is in line with their results. This could be due to two outlier patients in PICH group who spent 131 and 143 days in hospital. When these patients were removed from the analysis, mean cost of SAH exceeded that of PICH.

CE and LA strokes compared with SV and UC were predictors of increased total cost. As in previous studies, patients with CE stroke had more severe neurological deficits and poorer outcomes, resulting in greater resource utilization, relatively longer hospitalization and ICU LOS and higher medical costs,^{20,21} as opposed to SV stroke.

As shown elsewhere,^{10,14,22} we found that cost of acute care rose with stroke severity, this was mostly driven by increased LOS. However, when these same factors were examined in multivariable analysis, stroke severity emerged as an independent predictor of cost after accounting for LOS effects.

Cost and LOS are dependent of functional outcome at discharge. Similarly to other studies, they increased with higher mRS scores^{10,14} and lower BI scores.^{3,10} Similarly to high-income

countries,^{10,31} most patients (76%) were discharged home, however, more than half needed help. Patients were discharged from hospital mostly when their medical investigations were completed and their general medical condition was stable in order to continue domiciliary rehabilitation treatment.

Similarly to other middle-income studies' findings,^{17,18} the cost of patients who underwent a surgery or developed infectious complication was significantly higher, due to the added cost of operating room and surgeons' fees, extended hospital LOS and antibiotic treatments. Katzan et al. reported extended care and an incremental cost of US\$20,413 (2015 US\$) in stroke patients with pneumonia compared with infection-free patients.¹⁵

Patients who died in hospital had higher cost compared with survivors, as found elsewhere,¹⁴ however mortality rate in this study was considerably lower than other middle-income countries,⁴ but higher than some high-income countries^{20,22} yet very close to Greece.¹⁴ However, these former^{20,22} did not include hemorrhagic stroke patients, which show higher mortality rates than IS.³² Other possible reasons are the higher number of stroke severity in this study, the lack of stroke unit and the underuse of thrombolysis in Lebanese hospitals.

Lebanon has a highly fragmented health care system and pluralistic.³³ Many differences in health care system quality remain between rural and urban areas as well as between public and private health care with different types of managed healthcare plans. In Lebanon, 46.8% of the population reported having some form of insurance (either social or private).³³ If one excludes the non-Lebanese population that is estimated at 7.6%, the government is responsible for the remaining 45.6% of the population.³³ The total contribution of the public TPPs represented approximately 45% (US\$634626) of the total cost. TPP type significantly influenced total cost. In fact, in Lebanon, the cost of each resource varies based on TPP coverage tariffs. Public payers have lower tariffs for the same resource use compared to private.

Strengths and limitations of this study

The first strength of this study was related to the prospective data collection using validated tools used in previous similar research for data collection. It pioneered in assessing cost of stroke predictors through multivariable analysis. Additionally, we estimated costs, including physicians' fees, based on actual bills vs. using proxy methods, rather than predetermined charges. We conducted a multicenter incidence-base study including a diversified population, hence increasing the generalizability of our results.

This study does, however, have limitations. Even though patients came from all governorates, hospitals were limited to Beirut region. In this study, we could not exclude some unintentional bias in patient care, due to its observational nature. Also, we did not have strict guidelines for the clinical management of patients, which depended primarily on the physician in charge.

Conclusion

This study is an important first step in evaluating the economic impact of hospitalization due to stroke in Lebanon. Cost of care is significantly influenced by level of stroke severity and LOS. This information may help policy makers to develop health care plans to minimize economic burden on health system. Future studies should focus on modifiable, often unmeasured parameters, related not only to stroke characteristics, but also to hospital operational policies, potentially influencing LOS. Because stroke often results in permanent dependence, cost analysis of long-term care from a societal perspective should be established.

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Conflicts of interest

All authors declare that they have no conflict of interest.

Table 1. Demographic characteristics.

	All (n=203;100%)	IS (n=161;79.3%)	TIA (n=12;5.9%)	PICH (n=14;6.9%)	SAH (n=16;7.9%)	P-value
Age (mean±SD)	68.8±12.9	70.3±12.3	62.3±16.0	72.6±9.4	55.0±9.9	<0.001 ^a
Gender–Male (n(%))	117(57.6%)	96(59.6%)	8(66.7%)	9(64.3%)	4(25.0%)	0.048
TPP						NS
Public	166(81.8%)	129(80.1%)	11(91.7%)	11(78.6%)	15(93.8%)	
Private	37(18.2%)	32(19.9%)	1(8.3%)	3(21.4%)	1(6.3%)	
Marital status						NS*
Single/ Divorced	19(9.4%)	13(8.1%)	1(8.3%)	3(21.4%)	2(12.5%)	
Widowed	62(30.5%)	54(33.5%)	2(16.7%)	2(14.3%)	4(25.0%)	
Married	122(60.1%)	94(58.4%)	9(75.0%)	9(64.3%)	10(62.5%)	
Education						NS*
Illiterate	37(18.2%)	34(21.1%)	1(8.3%)	1(7.1%)	1(6.3%)	
Elementary	86(42.4%)	67(41.6%)	4(33.3%)	7(50.0%)	8(50.0%)	
Secondary	35(17.2%)	27(16.8%)	4(33.3%)	2(14.3%)	2(12.5%)	
≥High school	45(22.2%)	33(20.5%)	3(25.0%)	4(28.5%)	5(31.3%)	
Professional condition						NS*
Employed	61(30.0%)	46(28.6%)	5(41.7%)	6(42.9%)	4(25.0%)	
Housewife	82(40.4%)	63(39.1%)	4(33.3%)	4(28.6%)	11(68.8%)	
Retired	21(10.3%)	16(9.9%)	1(8.3%)	4(28.6%)	0(0%)	
Unemployed	39(19.2%)	36(22.4%)	2(16.7%)	0(0%)	1(6.3%)	
Monthly home income (US\$)						NS*
<500	60(29.6%)	52(32.3%)	2(16.7%)	2(14.3%)	4(25.0%)	
[500-1,000]	62(30.5%)	48(29.8%)	5(41.7%)	5(35.7%)	4(25.0%)	
[1,000-1,500]	37(18.2%)	26(16.1%)	2(16.7%)	3(21.4%)	6(37.5%)	
>1,500	44(21.7%)	35(21.7%)	3(25.0%)	4(28.6%)	2(12.5%)	

IS=ischemic stroke; TIA=transit ischemic attack; PICH=primary intracerebral hemorrhage; SAH=subarachnoid hemorrhage, TPP=third party payer.

*Non-parametric test

^aSAH vs. PICH and SAH vs. IS

Table 2. Clinical characteristics.

	All (n=203;100%)	IS (n=161;79.3%)	TIA (n=12;5.9%)	PICH (n=14;6.9%)	SAH (n=16;7.9%)	P-value
Risk factors						
-Hypertension	153(75.7%)	126(78.3%)	10(83.3%)	10(76.9%)	7(43.8%)	0.020
-Dyslipidemia	76(37.6%)	60(37.3%)	9(75.0%)	4(30.8%)	3(18.8%)	0.020
-Diabetes Mellitus	83(41.1%)	70(43.5%)	4(33.3%)	7(58.3%)	2(12.5%)	NS
-Atrial Fibrillation	26(12.9%)	22(13.7%)	3(25.0%)	1(7.7%)	0(0%)	NS
-Smoker						NS*
▪former smoker	31(15.3%)	24(14.9%)	3(25.0%)	4(28.6%)	0 (0%)	
▪current smoker	102(50.5%)	82(50.9%)	5(41.7%)	4(28.6%)	11(68.8%)	
First ever stroke/TIA	171(84.2%)	132(82.0%)	11(91.7%)	12(85.7%)	0(0%)	NS
Pre-stroke BI (mean±SD)	98.7±3.0	98.8±3.0	98.3±3.3	97.9±3.8	99.4±1.7	NS
NIHSS on admission (mean±SD)	10.8±9.9	10.0±8.6	0.7±1.0	19.4±12.3	19.7±12.7	<0.001* a
LOS (mean±SD)	12.9±18.5	9.9±8.8	3.4±1.6	37.4±46.9	30.1±28.3	<0.001* b
ICU admission	107(52.7%)	78(48.4%)	1(8.3%)	12(85.7%)	16(100%)	<0.001
ICU LOS (mean±SD)	5.9±13.2	3.6±6.8	0.2±0.6	20.2±32.2	20.8±20.9	<0.001* c
mRS at discharge (mean±SD)	3.5±2.0	3.5±1.9	0.6±0.9	4.5±1.8	4.6±1.1	<0.001* c
BI at discharge (mean±SD)	58.6±38.8	58.5±38.1	97.9±4.5	38.0±43.8	38.5±35.1	<0.001* c
TOAST classification						0.014*
LA	37(21.4%)	36(22.4%)	1(8.3%)			
CE	55(31.8%)	53(32.9%)	2(16.7%)			
SV	27(15.6%)	27(16.8%)	0(0%)			
UC	54(31.2%)	45(27.9%)	9(75.0%)			
Discharge destination						<0.001*
Home	72(35.5%)	56(34.8%)	12(100%)	3(21.4%)	1(6.3%)	
Home with help	82(40.4%)	69(42.9%)	0(0%)	5(35.7%)	8(50.0%)	
Rehabilitation center/Nursing home	22(10.8%)	16(9.9%)	0(0%)	2(14.3%)	4(25.0%)	
Death	27(13.3%)	20(12.4%)	0(0%)	4(28.6%)	3(18.8%)	
Cost (US\$) (mean±SD)/median(25th-75th)	6961±15663 2751(1484-6396)	4248±4352 2578(1492-5436)	1277±492 1234(947-1436)	26,698±50,400 8028(2382-28462)	21,257±14,625 14,746(1206-23957)	<0.001* d

IS=ischemic stroke; TIA=transit ischemic attack; PICH=primary intracerebral hemorrhage; SAH=subarachnoid hemorrhage, LOS=length of stay; ICU=intensive care unit; NIHSS= National Institution of Health Stroke Scale; mRS=modified Rankin Scale; BI=Barthel Index; TOAST=Trials of Org 10172 in Acute Stroke Treatment; LA=large-artery atherosclerosis; CE=cardioembolism; SV=small-vessel occlusion; UC=unclassified.

*Non-parametric test

^aExcept SAH vs. PICH

^bExcept SAH vs. PICH and TIA vs. IS

^cTIA vs. IS; PICH and SAH

^dExcept SAH vs. PICH

Table 3. Bivariable analysis for hospital LOS, ICU LOS and cost of stroke.

	N	LOS	ICU LOS	Cost (US\$)	P-value [~]
Total	203	12.9±18.5	5.9±13.2	6961±15663	-
Type of stroke					<0.001 ^a
IS	161	9.8±8.8	3.6±6.8	4248±4352	
TIA	12	3.4±1.6	0.2±0.6	1277±492	
PICH	14	37.3±46.9	20.2±32.2	26698±50400	
SAH	16	30.1±28.3	20.8±20.9	21257±14625	
NIHSS					<0.001 ^b
No stroke symptoms	13	5.1±4.7	2.5±4.7	3049±3764	
Minor stroke	63	4.8±3.0	0.7±1.7	2372±2214	
Moderate stroke	67	11.1±16.0	2.8±3.8	4451±5129	
Moderate/Severe stroke	18	14.7±10.9	7.8±10.3	7049±5764	
Severe stroke	42	29.7±28.0	18.7±23.4	19021±30734	
mRS					<0.001 [*]
Independent	61	4.4±2.8	0.8±2.5	1971±1741	
Dependent	115	14.9±18.4	5.6±9.1	7195±9647	
Dead	27	23.7±29.0	18.6±27.2	17237±36370	
BI					<0.001 ^c
Independence	49	4.3±2.5	0.6±1.9	1853±1263	
Mild dependence	32	5.2±3.3	1.4±3.2	2405±2070	
Moderate dependence	30	8.3±5.0	3.3±4.2	4779±4762	
Severe dependence	65	20.9±22.4	7.9±11.2	9793±11753	
BS					<0.001 ^{#d}
LACS	27	5.0±2.8	0.4±0.9	1827±1092	
POCS	31	10.5±8.6	5.6±8.7	4365±4188	
TACS	5	13.6±6.6	7.4±3.5	5732±1819	
PACS	96	10.9±9.8	3.6±6.9	4896±4854	
POCS+PACS	2	4.0±1.4	0±0	1546±107	
First ever vs. recurrent stroke					NS
First ever	171	13.8±19.9	6.5±14.2	7495±16975	
Recurrent	32	8.6±5.2	2.7±4.1	4107±2914	
Infection status					<0.001
Infection(-)	141	6.6±4.9	2.1±3.9	3192±3459	
Infection(+)	62	27.2±27.8	14.5±20.8	15532±26028	

	N	LOS	ICU LOS	Cost (US\$)	P-value[~]
Total	203	12.9±18.5	5.9±13.2	6961±15663	-
Surgery					<0.001
Surgery(-)	175	9.8±13.2	3.4±6.8	4335±6421	
Surgery(+)	28	32.3±31.4	21.3±26.7	23374±35295	
Gender					0.015 ^e
Male	117	12.6±20.8	5.6±14.5	6624±19009	
Female	86	13.3±14.8	6.2±11.2	7419±9462	
TPP					0.039 ^e
Private	37	13.7±19.6	5.9±13.4	8583±13061	
Public	166	12.8±18.3	5.6±12.1	6599±16199	
TOAST					<0.001 ^{#f}
LA	37	10.2±8.9	2.6±3.7	4166±2721	
CE	55	12.7±10.2	6.0±8.4	6064±5865	
SV	27	5.0±2.8	0.4±1.0	1827±1092	
UC	54	7.6±7.5	2.5±7.0	3003±3251	
Discharge destination					<0.001 ^{*g}
Home	72	4.5±2.7	0.7±2.3	1950±1607	
Home with help	82	12.5±12.9	5.6±9.5	6555±8864	
Rehabilitation center/Nursing home	22	23.7±29.0	7.8±9.5	12258±12591	
Death	27	28.9±30.3	18.6±27.2	17237±36370	

(mean±SD)

IS=Ischemic stroke; TIA=Transit Ischemic Attack; PICH=Primary Intracerebral hemorrhage; SAH=Subarachnoid hemorrhage, LOS=length of stay; ICU=intensive care unit; TPP=third party payer; NIHSS= National Institution of Health Stroke Scale; mRS=modified Rankin Scale; BI=Barthel Index; TOAST=Trials of Org 10172 in Acute Stroke Treatment; LA=large-artery atherosclerosis; CE=cardioembolism; SV=small-vessel occlusion; UC=unclassified; LACS=lacunar stroke syndrome; PACS=partial anterior circulation stroke; POCS=posterior circulation stroke; TACS=total anterior circulation stroke.

[~]For ICU LOS, non-parametric tests were used as the distribution couldn't be normal. LOS and cost were treated as ln(LOS) and ln(cost), parametric tests were used unless noted.

*Non-parametric test used (due to non-homogeneity of variances)

[#]Non-parametric test used, except for LOS (due to its homogeneity of variances)

^aNS for SAH vs. PICH

^bLOS: NS for no stroke symptoms vs. minor stroke and moderate stroke vs. moderate/severe stroke / ICU LOS: only for severe stroke vs. everything else / Cost: NS for no stroke symptoms vs. minor stroke and moderate stroke, moderate stroke vs. moderate/severe stroke

^cLOS and cost: NS for independence vs. mild dependence / ICU LOS: NS for independence vs. mild and moderate dependence and mild vs. moderate dependence

^dOnly for LACS vs. POCS, PACS and TACS

^eOnly for cost, NS for LOS and ICU LOS

^fLOS: NS for SV vs. UC, CE vs. LA, and LA vs. UC / ICU LOS: NS for LA vs. SV, LA vs. UC, SV vs. UC / Cost: NS for LA vs. UC and SV vs. UC

^gLOS and cost: NS for rehabilitation center/nursing home vs. death / ICU LOS: NS for home with help vs. rehabilitation center/nursing home.

Table 4. Multivariable linear regression analysis of overall hospital length of stay and cost for all type of strokes and for ischemic strokes.

	All type of strokes ^a					Ischemic strokes ^b					Hospital LOS ^c				
Variables explained	77.8% of the variance of total cost (ln(cost))					71.3% of the variance of total cost (ln(cost))					73.4% of the variance of total LOS (ln(LOS))				
Anova	<0.001					<0.001					<0.001				
Independent variables	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF	Unstandardized Coefficients		Standardized Coefficients	P-value	VIF
	B	SD				B	SD				B	SD			
(Constant)	6.240					7.281					0.799				
LOS	0.013	0.003	0.218	<0.001	2.6	0.038	0.006	0.400	<0.001	1.9					
ICU LOS	0.026	0.008	0.213	0.001	3.2	0.061	0.010	0.351	<0.001	1.6	0.033	0.006	0.295	<0.001	2.1
TPP				<0.001	1.0				<0.001	1.0					
Public	-	-	-			-	-	-							
Private	0.444	0.089	0.181			0.529	0.086	0.284							
Surgery	0.609	0.135	0.208	<0.001	1.7						0.416	0.129	0.155	0.001	1.5
Type of stroke															
IS+TIA	-	-	-	0.019	1.8										
PICH+SAH	0.320	0.135	0.114												
NIHSS at admission	0.100	0.046	0.117	0.032	2.3						0.116	0.046	0.148	0.013	2.3
mRS at discharge	0.109	0.026	0.207	<0.001	1.9						0.145	0.027	0.300	<0.001	2.1
Infectious complication	0.264	0.105	0.116	0.013	1.7						0.376	0.104	0.180	<0.001	1.6

	All type of strokes ^a					Ischemic strokes ^b					Hospital LOS ^c				
BI at discharge						-0.003	0.001	-0.164	0.005	1.6					
TOAST classification															
LA/CE						-	-	-	0.005	1.2					
UC/SV						-0.207	0.073	-0.142							
Discharge destination															
Home (with or without help)											-	-	-	<0.001	1.3
Rehabilitation center/Nursing home/Death											0.419	0.116	0.159		
Sex (male reference)											-0.160	0.074	-0.090	0.033	1.2

IS=Ischemic stroke; TIA=Transit Ischemic Attack; PICH=Primary Intracerebral hemorrhage; SAH=Subarachnoid hemorrhage, LOS=length of stay; ICU=intensive care unit; TPP=third party payer; NIHSS= National Institution of Health Stroke Scale; mRS=modified Rankin Scale; BI=Barthel Index; TOAST=Trial of Org 10172 in Acute Stroke Treatment; LA=large-artery atherosclerosis; CE=cardioembolism; SV=small-vessel occlusion; UC=unclassified; LACS=lacunar stroke syndrome; PACS=partial anterior circulation stroke; POCS=posterior circulation stroke; TACS=total anterior circulation stroke.

^a Dependent variable: ln(cost)

Independent variables: LOS, ICU LOS, TPP, Surgery, Type of stroke, NIHSS at admission, mRS at discharge, Infectious complication, BI at discharge, Discharge destination, Sex, Age

^b Dependent variable: ln(cost)

Independent variables: LOS, ICU LOS, TPP, Surgery, NIHSS at admission, mRS at discharge, Infectious complication, BI at discharge, TOAST classification, Discharge destination, Sex, Age, Bamford classification (LACS vs. other)

^c Dependent variable: ln(LOS)

Independent variables: ICU LOS, TPP, Surgery, Type of stroke, NIHSS at admission, mRS at discharge, Infectious complication, BI at discharge, Discharge destination, Sex, Age

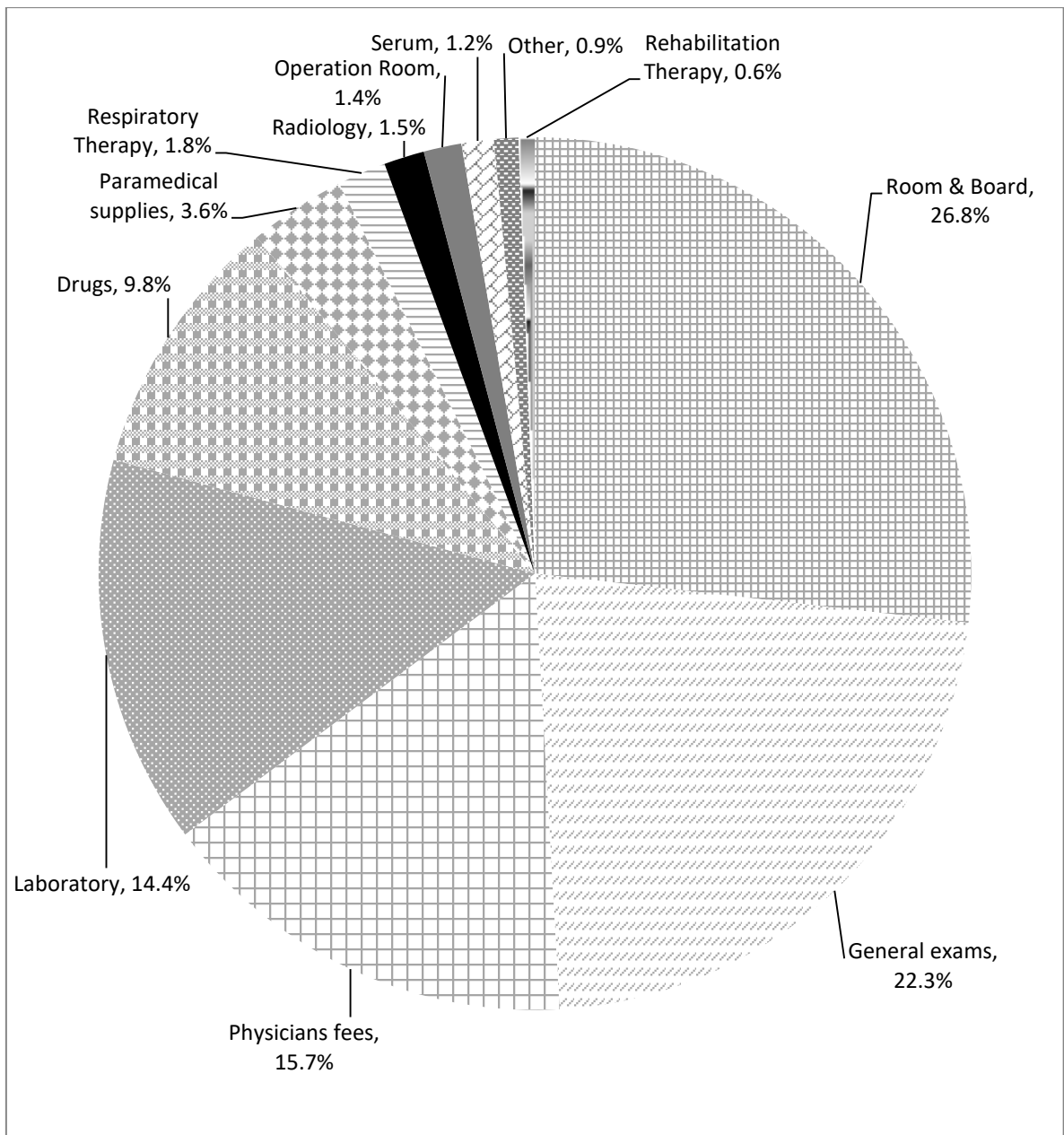


Figure 1. In-hospital cost distribution.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*. 2012;380(9859):2095–128.
2. Donnan GA, Fisher M, Macleod M, et al. Stroke. *Lancet* 2008;371(9624):1612–1623.

3. Fattore G, Torbica A, Susi A, et al. The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC Neurol.* 2012;12:137.
4. Asil T, Celik Y, Sut N, et al. Cost of acute ischemic and hemorrhagic stroke in Turkey. *ClinNeurolNeurosurg.* 2011;113(2):111-4.
5. Ovbiagele B, Goldstein LB, Higashida RT, et al. American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke.* 2013;44(8):2361-75.
6. Lubitz J, Prihoda R. The use and costs of Medicare services in the last 2 years of life. *Health Care Financ Rev* 1984;5:117–31.
7. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009;40:2276.
8. Meijer R, van Limbeek J, de Haan R. Development of the stroke-unit discharge guideline: choice of assessment instruments for prediction in the subacute phase post-stroke. *Int J Rehabil Res.* 2006;29(1):1–8.
9. Bank of Beirut. **[online]** Available at: www.bdl.gov.lb/statistics/table.php?name%405282usd (accessed 11 March 2016)

10. Alvarez-Sabín J, Quintana M, Masjuan J, et al. Economic impact of patients admitted to stroke units in Spain. *The European Journal of Health Economics*. 2016. DOI: 10.1007/s10198-016-0799-9
11. The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1998;28:2119–2125.
12. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.
13. Oxford Stroke Classification. **[online]** Available at: <<http://www.medquarterly.com/mq88/MQPDF/MM/OxfordStrokeClassification.pdf>> (accessed 11 November 2015)
14. Gioldasis G, Talelli P, Chroni E, et al. In-hospital direct cost of acute ischemic and hemorrhagic stroke in Greece. *Acta Neurol Scand* 2008;118:268–274.
15. Katzan IL, Dawson NV, Thomas CL, et al. The cost of pneumonia after acute stroke. *Neurology* 2007;68:1938–43.
16. Khealani BA, Javed ZF, Syed NA, et al. Cost of acute stroke care at a tertiary care hospital in Karachi, Pakistan. *J Pak Med Assoc*. 2003;53(11):552-5.
17. Christensen MC, Valiente R, Silva Sampaio G. Acute treatment costs of stroke in Brazil. *Neuroepidemiology* 2009;32:142–9.
18. Christensen MC, Previgliano I, Capparelli FJ. Acute treatment costs of intracerebral hemorrhage and ischemic stroke in Argentina. *Acta Neurol Scand* 2009;119:246–53.
19. Claesson L, Gosman-Hedstrom G, Johannesson M, et al. Resource utilization and costs of stroke unit care integrated in a care continuum: a 1-year controlled, prospective, randomized study in elderly patients: the Göteborg 70+ Stroke Study. *Stroke*. 2000;31:2569–77.
20. Yoneda Y, Uehara T, Yamasaki H, et al. Hospital based study of the care and cost of acute ischemic stroke in Japan. *Stroke* 2003;34:718–24.

21. Caro JJ, Huybrechts KF, Duchesne I. Management patterns and costs of acute ischemic stroke: an international study. For the Stroke Economic Analysis Group. *Stroke*. 2000;31(3):582-90.
22. Diringner MN, Edwards DF, Mattson DT, et al. Predictors of acute hospital costs for treatment of ischemic stroke in an academic center. *Stroke*. 1999;30:724–728.
23. Reed SD, Blough DK, Meyer K, et al. Inpatient costs, length of stay, and mortality for cerebrovascular events in community hospitals. *Neurology*. 2001;57:305–314
24. Grieve R, Hutton J, Bhalla A, et al. A comparison of the costs and survival of hospital-admitted stroke patients across Europe. *Stroke* 2001;32:1684–91.
25. Mamoli A, Censori B, Casto L, et al. An analysis of the costs of ischemic stroke in an Italian stroke unit. *Neurology*. 1999;53(1):112-6.
26. Wentworth DA, Atkinson RP. Implementation of an acute stroke program decreases hospitalization costs and length of stay. *Stroke*. 1996;27:1040–3.
27. Briggs DE, Felberg RA, Malkoff MD, et al. Should mild or moderate stroke patients be admitted to an intensive care unit? *Stroke*. 2001;32:871–6.
28. Holloway RG, Witter Jr. DM, Lawton KB, et al. Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology*. 1996;46:854–860.
29. Yoneda Y, Okuda S, Hamada R, et al. Hospital cost of ischemic stroke and intracerebral hemorrhage in Japanese stroke centers. *Health Policy* 2005;73:202–11.
30. Dodel RC, Haacke C, Zamzow K et al. Resource utilization and costs of stroke unit care in Germany. *Value Health* 2004;7:144–52.
31. van Eeden M, van Heugten C, van Mastriigt GAPG, et al. The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year post stroke. *BMJ Open* 2015;5:e008220. doi:10.1136/bmjopen-2015-008220
32. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart

- Association/ American Stroke Association Stroke Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Circulation*. 2007;116(16):391-413
33. Ammar W, Fakha H, Azzam O, et al. Lebanon National Health Accounts. World Bank:2010
[online] Available at: <http://siteresources.worldbank.org/INTHSD/Resources/376278-1261143298590/6660179-1280173228245/LebanonNHA.pdf> (accessed 24 May 2018)

5. Discussion

5.1 Discussion of the main results of the thesis

In Lebanon, we found that stroke management is in line with evidence-based and clinical practice guidelines. However reperfusion therapy are still largely underused and remains a major challenge in achieving guideline-based reperfusion goals. In Lebanon, mortality due to stroke is relatively high compared to other countries (specially the short-term mortality). Public awareness campaigns (focusing on people with low education and SES) of stroke risk factors, warning symptoms, and importance of immediate modern concepts of time-dependent stroke treatment are needed. The implementation of stroke unit at the hospitals, as well as stroke management protocols, will be important steps toward improving the standard of care (both clinically and economically). This may limit the mortality rate and possible complications after stroke.

More aggressive control of modifiable risk factors and needed in order the reduce stroke incidence and therefore stroke mortality. HT is an important factor in primary prevention for several reasons. HT is the most powerful risk factor for stroke, its prevalence is high in Lebanon and the management of hypertensive patients remains suboptimal. Thus, better management of hypertensive patients will reduce the risk of stroke.

Improving rehabilitation in-hospital and highlighting the importance of rehabilitation after discharge is crucial for patients in order to improve their physical function impairments and reintegrate socially and professionally in the society. This will diminish the decline in QOL post-stroke that was relatively high in our study and therefore restrict the post-stroke depression rate. Being able to continue working after a stroke is crucial for the individual and the society, this will decrease the indirect costs (loss work productivity as well as loss of future productivity) and DALYs.

Overall in-hospital stroke management did not differ between SES and private vs. public third party payer even though the in-hospital cost of stroke significantly differed. This means that patients receive the same care regardless of their SES and third party payer coverage.

The sum of all these measures (incidence, prevalence, mortality, QOL, cost of illness, etc.) would give a complete picture of the burden of stroke in Lebanon.

5.2 Implications of outcomes for public health policy makers

Our findings are important for health professionals and public health policy makers. When reliable data on stroke burden are available, health care planning can be more effectively undertaken, ideally with the generation of longitudinal data to usefully monitor the effectiveness of any interventions. Our findings reinforce the evidence for resource allocation for primary and secondary prevention programs and awareness campaigns on the danger of behavioral risk factors to reduce stroke morbidity and mortality.

6. Perspectives & Conclusion

Stroke is given currently a lower priority for clinical services and research compared with other diseases with a similar or lower public health impact. This is related to the lack of readily accessible comparative data to help mount a political case for the development of national strategies to address the burden of stroke. In the near future, it would be interesting to:

Calculate exactly the incidence rate of stroke in Lebanon.

Analyze the regional disparities in the epidemiology of stroke and their influence on risk factors and the management of the disease.

Assess the knowledge of stroke symptoms and risk factors and attitude of the population toward stroke.

Estimate the cost-effectiveness of integrated specialized stroke units in Lebanon: providing enhanced patient outcomes compared with conventional care.

Evaluate the chronic management of stroke: secondary prevention (assessing short-term and long-term medication compliance of stroke patients to treatment, medical follow-up, routine examinations, control of risk factors among patients, stroke recurrence rate, etc.), chronic rehabilitative care, late mortality rate and disability prevalence.

Research for more efficacious therapeutic options to prevent stroke sequelae are crucially needed. This includes the use of stem cells, and the search for new neuroprotective agents.

More research in the areas of hypothermia (therapeutic cooling), stem cell therapies, and a polypill for secondary prevention of stroke are needed.

Another interesting topic is to determine the quality of life of caregivers of stroke patients and its determinants. Moreover, determining the depression rate of caregivers of stroke patients and its determinants may be reasonable.

The studies presented in this manuscript may possibly be repeated but in a way that allows their generalizability to the whole country (better sampling of all governorates, larger sample size, etc.) in the community and not just hospitals, measuring socio-economic risk factors (education, work, income), psychic factors (stress and anxiety), all comorbidities and potential risk factors.

It is absolutely necessary to develop our knowledge of the epidemiology of stroke in Lebanon, in order to limit the impact and burden of the disease in the years to come.

7. REFERENCES

A

- Abou-Chebl A. Intra-arterial Therapy for Acute Ischemic Stroke. *Neurotherapeutics*. 2011;8(3):400-413.
- Abubakar SA, Isezuo SA. Health Related Quality of Life of Stroke Survivors: Experience of a Stroke Unit. *International Journal of Biomedical Science : IJBS*. 2012;8(3):183-187.
- Adams HP, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999 Jul 13; 53(1):126–31.
- Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
- Albertsen IE, Rasmussen LH, Lane DA, et al. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation. *Chest*. 2014;145:559–566.
- Alexander DD, Bylsma LC, Vargas AJ, et al. Dairy consumption and CVD: a systematic review and meta-analysis. *Br J Nutr*. 2016;115:737–750.
- Amarenco P, Labreuche J, Touboul PJ. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. *Atherosclerosis*. 2008;196:489–496.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus [published correction appears in *Diabetes Care*. 2010;33:e57 *Diabetes Care*. 2010;33(suppl 1):S62–S69.
- American Heart Association/American Stroke Association. Ischemic Strokes (Clots). 2018. Available at: <https://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/IschemicClots/Ischemic-Strokes-Clots_UCM_310939_Article.jsp> (Accessed on 13 August 2018)
- American Heart Association/American Stroke Association. Ischemic Strokes (Clots). 2018. Available at: <https://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/HemorrhagicBleeds/Hemorrhagic-Strokes-Bleeds_UCM_310940_Article.jsp> (Accessed on 13 August 2018)
- American Heart Association/American Stroke Association. Stroke Fact Sheet. 2017. Available at: <https://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@hcm/@sta/documents/downloadable/ucm_462739.pdf> (Accessed on 13 August 2018)
- American Heart Association/American Stroke Association. Stroke risks. Available at: <https://www.strokeassociation.org/STROKEORG/AboutStroke/UnderstandingRisk/Understanding-Stroke-Risk_UCM_308539_SubHomePage.jsp> (Accessed on 13 August 2018)
- American Heart Association/American Stroke Association. Stroke, TIA and warning signs. Available at: <http://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@hcm/@sta/documents/downloadable/ucm_309532.pdf> (Accessed on 13 August 2018)

American Thoracic Society. Sickness Impact Profile. 2007. Available at: <<http://www.atsqol.org/sections/instruments/pt/pages/sick.html>>. (Retrieved 30 March 2009)

Araji AA, Sawaya HR, Sawaya RA. Gene mutations and stroke in the young adult. *J Stroke Cerebrovasc Dis*. 2014 Nov-Dec;23(10):2554-8.

Asil T, Celik Y, Sut N, et al. Cost of acute ischemic and hemorrhagic stroke in Turkey. *Clin Neurol Neurosurg*. 2011;113(2):111-114.

Atrial Fibrillation investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994 Jul 11. 154(13):1449-57.

Appelros P, Stegmayr B, Terént A. Sex Differences in Stroke Epidemiology A Systematic Review. *Stroke*. 2009 Apr 1; 40(4):1082–90.

Armstrong ME, Green J, Reeves GK, et al. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation*. 2015;131:721–729.

Assessment methods for stroke patients. in: AHCPR poststroke rehabilitation: clinical practice guidelines. Aspen Publishers; 1996.

Aström M, Asplund K, Aström T. Psychosocial function and life satisfaction after stroke. *Stroke* 1992;23:527-31.

Avgil Tsadok M, Jackevicius CA, Rahme E, et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA*. 2012;307:1952–1958.

B

Baillargeon JP, McClish DK, Essah PA, et al. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005;90:3863–3870.

Bamford J, Sandercock P, Jones L, et al. The natural history of lacunar infarction: The Oxfordshire Community Stroke Project. *Stroke* 1987;18:545-551.

Bath PMW, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005;330(7487):342.

Bejot Y, Catteau A, Caillier M, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. *Stroke*. 2008 Jul. 39(7):1945-51.

Bell EJ, Lutsey PL, Windham BG, et al. Physical activity and cardiovascular disease in African Americans in Atherosclerosis Risk in Communities. *Med Sci Sports Exerc*. 2013;45:901–907.

Bergner M, Bobbitt RA, Carter WB, et al. The Sickness Impact Profile: development and final revision of a health status measure. *Medical Care*. 1981;19(8), 787-805.

Bernstein AM, de Koning L, Flint AJ, et al. Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr*. 2012;95:1190–1199.

Bevan S, Traylor M, Adib-Samii P, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genome-wide associations. *Stroke*. 2012;43:3161–3167.

Bhat VM, Cole JW, Sorkin JD, et al. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008;39:2439–2443.

Biffi A, Sonni A, Anderson CD, et al. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. *Ann Neurol*. 2010;68:934–943.

Blomstrand A, Blomstrand C, Ariai N, et al. Stroke incidence and association with risk factors in women: a 32-year follow-up of the Prospective Population Study of Women in Gothenburg. *BMJ Open*. 2014;4:e005173.

Blucher A, Devan WJ, Holliday EG, et al. Heritability of young- and old-onset ischaemic stroke. *Eur J Neurol*. 2015;22:1488–1491.

Boardman HMP, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev*. 2015 Mar 10; 3:CD002229.

Bowman TS, Sesso HD, Ma J, et al. Cholesterol and the risk of ischemic stroke. *Stroke*. 2003;34:2930–2934.

Broadley SA, Jørgensen L, Cheek A, et al. Early investigation and treatment of obstructive sleep apnoea after acute stroke. *J Clin Neurosci*. 2007;14:328–333.

Brown DL, Mowla A, McDermott M, et al. Ischemic stroke subtype and presence of sleep-disordered breathing: the BASIC sleep apnea study. *J Stroke Cerebrovasc Dis*. 2015;24:388–393.

Buck D, Jacoby A, Massey A, et al. Evaluation of measures used to assess quality of life after stroke. *Stroke* 2000;31;2004-10.

Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1545–1588.

C

Callaly E, Ni Chroinin D, Hannon N, et al. Rates, predictors, and outcomes of early and late recurrence after stroke: the North Dublin Population Stroke Study. *Stroke*. 2016;47:244–246.

Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012 Nov. 33 (21):2719-47.

Cancelli I, Janes F, Gigli GL, et al. Incidence of transient ischemic attack and early stroke risk: validation of the ABCD2 score in an Italian population-based study. *Stroke*. 2011;42:2751–2757.

Casper ML, Nwaise IA, Croft JB, et al. Atlas of Stroke Hospitalizations Among Medicare Beneficiaries. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.

Casper ML, Wing S, Anda RF, et al. The shifting stroke belt: changes in the geographic pattern of stroke mortality in the United States, 1962 to 1988. *Stroke*. 1995;26:755–760.

CDC Centers for Disease Control and Prevention. Hookahs. Available at: <https://www.cdc.gov/tobacco/data_statistics/fact_sheets/tobacco_industry/hookahs/index.htm> (Accessed on 7 September 2018)

Centers for Disease Control and Prevention (CDC) Prevalence of stroke: United States, 2006–2010. *MMWR Morb Mortal Wkly Rep*. 2012;61:379–382.

Chamieh MC, Moore HJ, Summerbell C, et al. Diet, physical activity and socio-economic disparities of obesity in Lebanese adults: findings from a national study. *BMC Public Health*. 2015;15:279.

Chauhan G, Debette S. Genetic Risk Factors for Ischemic and Hemorrhagic Stroke. *Current Cardiology Reports*. 2016;18(12):124.

Cheng P, Wang J, Shao W. Monounsaturated fatty acid intake and stroke risk: a meta-analysis of prospective cohort studies. *J Stroke Cerebrovasc Dis*. 2016;25:1326–1334.

Chowdhury R, Stevens S, Gorman D, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *BMJ*. 2012;345:e6698.

Christensen MC, Previgliano I, Capparelli FJ. Acute treatment costs of intracerebral hemorrhage and ischemic stroke in Argentina. *Acta Neurol Scand*. 2009;119:246-253.

Christensen MC, Valiente R, Silva Sampaio G. Acute treatment costs of stroke in Brazil. *Neuroepidemiology*. 2009;32:142-149.

Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in “low risk” patients with a non-recent transient ischaemic attack. *J Neurol Neurosurg Psychiatry*. 2003;74:577–580

Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.

D

D’Elia L, Iannotta C, Sabino P, et al. Potassium-rich diet and risk of stroke: updated meta-analysis. *Nutr Metab Cardiovasc Dis*. 2014;24:585–587.

D’Agostino RB, Wolf PA, Belanger AJ, et al. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke*. 1994 Jan;25(1):40-3.

Dagres N, Nieuwlaat R, Vardas PE, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol*. 2007;49:572–577.

Dehlendorff C, Andersen KK, Olsen TS. Sex disparities in stroke: women have more severe strokes but better survival than men. *J Am Heart Assoc*. 2015;4:e001967.

del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke*. 1998 Jan;29(1):4-11.

Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. *Atherosclerosis*. 2013;229:489–495.

Dong JY, Zhang YH, Tong J, et al. Depression and risk of stroke: a meta-analysis of prospective studies. *Stroke*. 2012;43:32–37.

Donnan GA, Fisher M, Macleod M, et al. *Lancet* 2008, 371(9624):1612–1623.

E

Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40:2276-2293

El Sayed MJ, El Zahran T, Tamim H. Acute Stroke Care and Thrombolytic Therapy Use in a Tertiary Care Center in Lebanon. *Emergency Medicine International*. 2014;2014:438737.

El-Hajj M, Salameh P, Rachidi S, et al. Development of a diagnosis score for stroke in the Lebanese population. *Clinical Epidemiology and Global Health* [internet] . 2018 . Available from: <[https://cegh.net/article/S2213-3984\(18\)30030-7/fulltext?code=cegh-site](https://cegh.net/article/S2213-3984(18)30030-7/fulltext?code=cegh-site)> (Accessed on 12 September 2018)

El-Hajj M, Salameh P, Rachidi S, et al. Development of a risk of stroke score in the Lebanese population. *Clinical Epidemiology and Global Health* [internet]. 2018. Available from: <<https://www.sciencedirect.com/science/article/pii/S2213398418300575>> (Accessed on 12 September 2018)

Elijovich L, Josephson SA, Fung GL, et al. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. *J Stroke Cerebrovasc Dis*. 2009;18:185–189.

Elkind MS, Hills NK, Glaser CA, et al. Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS Study. *Circulation*. 2016;133:732–741.

Eriksson M, Carlberg B, Eliasson M. The disparity in long-term survival after a first stroke in patients with and without diabetes persists: the Northern Sweden MONICA study. *Cerebrovasc Dis*. 2012;34:153–160.

Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet [published correction appears in *N Engl J Med*. 2014;370:886] *N Engl J Med*. 2013;368:1279–1290.

F

Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation*. 2005;112:1687–1691.

- Farah R, Zeidan RK, Chahine MN, et al. Prevalence of stroke symptoms among stroke-free residents: first national data from Lebanon. *Int J Stroke*. 2015;10 Suppl A100:83-8.
- Fattore G, Torbica A, Susi A, et al. The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC Neurol*. 2012;12:137.
- Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014 Jan 18; 383(9913):245-54.
- Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. *Neuroepidemiology*. 2015;45(3):161-76.
- Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. *Neurology*. 2010;74:588-593.
- Ferri CP, Schoenborn C, Kalra L, et al. Prevalence of stroke and related burden among older people living in Latin America, India and China. *J Neurol Neurosurg Psychiatry* 2011;82(10):1074-82.
- Flint AC, Banki NM, Ren X, et al. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke*. 2012;43:2788-2790.
- Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. *Stroke* 2004;35:212-227.
- Ford JA, MacLennan GS, Avenell A, et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr*. 2014;100:746-755.
- Foroud T, Koller DL, Lai D, et al. Genome-wide association study of intracranial aneurysms confirms role of Anril and SOX17 in disease risk. *Stroke*. 2012;43:2846-2852.
- Fox CS, Golden SH, Anderson C, et al. American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2015;132:691-718.
- Fox CS, Polak JF, Chazaro I, et al. Genetic and environmental contributions to atherosclerosis phenotypes in men and women: heritability of carotid intima-media thickness in the Framingham Heart Study. *Stroke*. 2003;34:397-401.
- Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, et al. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142-2152.
- Friberg J, Scharling H, Gadsbøll N, et al. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (the Copenhagen City Heart Study) *Am J Cardiol*. 2004;94:889-894.
- Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012 Jun. 33 (12):1500-10.

Furmonavičius T. Methodological aspects of health-related quality of life assessment. *Medicina (Kaunas)* 2004;40:509-16.

G

Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.

GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385:117–171.

Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2007;6:1063–1072.

Giles WH, Kittner SJ, Hebel JR, et al. Determinants of black-white differences in the risk of cerebral infarction: the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Arch Intern Med* 1995;155:1319–1324.

Gillum LA, Johnston SC. Oral contraceptives and stroke risk: the debate continues. *Lancet Neurol*. 2004;3:453–454.

Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA*. 2000;284:72–78.

Gioldasis G, Talelli P, Chroni E, et al. In-hospital direct cost of acute ischemic and hemorrhagic stroke in Greece. *Acta Neurol Scand*. 2008;118:268-274.

Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S74–S75]. *Circulation*. 2014;129(suppl 2):S49–S73.

Goldstein LB, Bushnell CD, Adams RJ, et al. TA American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2011;42:e26] *Stroke*. 2011;42:517–584.

Goldstein M, Barnett HJM, Orgogozo JM, et al. Stroke-1989: Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and Other Cerebrovascular Disorders. *Stroke* 1989;20:1407-1431

Grau AJ, Barth C, Geletneky B, et al. Association between recent sports activity, sports activity in young adulthood, and stroke. *Stroke*. 2009;40:426–431.

Gretarsdottir S, Thorleifsson G, Manolescu A, et al. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol*. 2008;64:402–409.

Gudbjartsson DF, Holm H, Gretarsdottir S, et al. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat Genet*. 2009;41:876–878.

Gustavsson A, Svensson M, Jacobi F, et al. CDBE2010 Study Group. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011 Oct;21(10):718-79.

H

- Haast RAM, Gustafson DR, Kiliaan AJ. Sex differences in stroke. *J Cereb Blood Flow Metab.* 2012 Dec; 32(12):2100–7.
- Hacke W, Kaste M, Bluhmki E, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008 Sep 25;359(13):1317-29.
- Hackett ML, Duncan JR, Anderson CS, et al. Health-related quality of life among long-term survivors of stroke: results from the Auckland Stroke Study. *Stroke* 2000; 31:440-7.
- Hankey G. Impact of treatment of people with transient ischaemic attacks on stroke incidence and public health. *Cerebrovasc Dis.* 1996;6:26–33.
- Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2015 Jul;46(7):2032-60.
- Henderson KM, Clark CJ, Lewis TT, et al. Psychosocial distress and stroke risk in older adults. *Stroke.* 2013;44:367–372.
- Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al. Effects of conjugated equine estrogen on stroke in the Women’s Health Initiative. *Circulation.* 2006;113:2425–2434.
- Hijazi Z, Oldgren J, Andersson U, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) sub-study. *Circulation.* 2012;125:1605–1616.
- Hillen T, Coshall C, Tilling K, et al. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. *Stroke.* 2003;34:1457–1463.
- Holzmann MJ, Aastveit A, Hammar N, et al. Renal dysfunction increases the risk of ischemic and hemorrhagic stroke in the general population. *Ann Med.* 2012;44:607–615.
- Hooker SP, Sui X, Colabianchi N, et al. Cardiorespiratory fitness as a predictor of fatal and nonfatal stroke in asymptomatic women and men. *Stroke.* 2008;39:2950–2957.
- Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women’s Pooling Project. *Stroke.* 2002;33:1863–1868.
- Hourihane JM, Clark WM. Clinical assessment and outcome scales in acute stroke. *Neuroimaging Clin North Am* 1999;9:539-52.
- Howard G, Anderson R, Johnson NJ, et al. Evaluation of social status as a contributing factor to the stroke belt region of the United States. *Stroke.* 1997;28:936–940.
- Howard G, Prineas R, Moy C, et al. Racial and geographic differences in awareness, treatment, and control of hypertension: the REasons for Geographic And Racial Differences in Stroke study. *Stroke.* 2006;37:1171–1178.
- Hu G, Sarti C, Jousilahti P, et al. Leisure time, occupational, and commuting physical activity and the risk of stroke. *Stroke.* 2005;36:1994–1999.
- Huo Y, Li J, Qin X, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA.* 2015;313:1325–1335.

Huxley RR, Barzi F, Lam TH, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. *Circulation*. 2011;124:2056–2064.

I

Imamura T, Doi Y, Arima H, et al. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. *Stroke*. 2009;40:382–388.

Intercollegiate Stroke Working Party. National clinical guideline for stroke, 5th edition. London:Royal College of Physicians 2016

International Stroke Genetics Consortium (ISGC), Wellcome Trust Case Control Consortium 2 (WTCCC2) Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke. *Nat Genet*. 2012;44:328–333.

J

Jackson CA, Mishra GD. Depression and risk of stroke in midaged women: a prospective longitudinal study. *Stroke*. 2013;44:1555–1560.

James AH, Bushnell CD, Jamison MG, et al. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol* 2005;106:509–516.

January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014 Dec 2. 130 (23):e199-267.

Jefferis BJ, Whincup PH, Papacosta O, et al. Protective effect of time spent walking on risk of stroke in older men. *Stroke*. 2014;45:194–199.

Johnson DA, Lisabeth L, Lewis TT, et al. The contribution of psychosocial stressors to sleep among African Americans in the Jackson Heart Study. *Sleep*. 2016;39:1411–1419.

Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *J Clin Sleep Med*. 2010;6:131–137.

Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *J Clin Sleep Med*. 2010;6:131–137.

Johnston SC, Fayad PB, Gorelick PB, et al. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology*. 2003;60:1429–1434.

Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901–2906.

Jones SB, Sen S, Lakshminarayan K, et al. Poststroke outcomes vary by pathogenic stroke subtype in the Atherosclerosis Risk in Communities Study. *Stroke*. 2013;44:2307–2310.

Jurjus AR, Tohme RA, Ephrem G, et al. Incidence and prevalence of circulatory diseases in Lebanon: a physician's inquiry. *Ethn Dis*. 2009;(19):1.

K

Kamel H, Navi BB, Nakagawa K, et al. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med*. 2011;39:554–559.

- Khealani BA, Javed ZF, Syed NA, et al. Cost of acute stroke care at a tertiary care hospital in Karachi, Pakistan. *J Pak Med Assoc*. 2003;53(11):552-555.
- Khoury JC, Kleindorfer D, Alwell K, et al. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke*. 2013;44:1500–1504.
- Kilarski LL, Achterberg S, Devan WJ, et al. Meta-analysis in more than 17,900 cases of ischemic stroke reveals a novel association at 12q24.12. *Neurology*. 2014;83:678–685.
- Kissela BM, Khoury J, Kleindorfer D, et al. Epidemiology of Ischemic Stroke in Patients With Diabetes The Greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care*. 2005 Feb 1; 28(2):355–9.
- Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79:1781–1787.
- Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke*. 2002;33:1321–1326
- Kittner SJ, Stern BJ, Feaser BR, et al. Pregnancy and the risk of stroke. *N Engl J Med*. 1996;335:768–774.
- Klein S, Burke LE, Bray GA, et al. American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2004;110:2952–2967.
- Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke*. 2005;36:720–723.
- Kleindorfer DO, Khoury J, Moomaw CJ, et al. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. *Stroke*. 2010;41:1326–1331.
- Krančiukaitė D, Rastenytė D. Measurement of quality of life in stroke patients. *Medicina (Kaunas)* 2006;42(9) 709
- Krarp LH, Truelsen T, Pedersen A, et al. Level of physical activity in the week preceding an ischemic stroke. *Cerebrovasc Dis*. 2007;24:296–300.
- Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health*. 2013;1:e259–e281.
- Krishnamurthi RV, Moran AE, Feigin VL, et al. Stroke Prevalence, Mortality and Disability-Adjusted Life Years in Adults Aged 20-64 Years in 1990-2013: Data from the Global Burden of Disease 2013 Study. *Neuroepidemiology*. 2015;45(3):190-202.
- Kurth T, Everett BM, Buring JE, et al. Lipid levels and the risk of ischemic stroke in women. *Neurology*. 2007;68:556–562.

L

- Lackland DT, Voeks JH, Boan AD. Hypertension and stroke: an appraisal of the evidence and implications for clinical management. *Expert Rev Cardiovasc Ther*. 2016;14:609–616.
- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises, part I: aging arteries: a “set up” for vascular disease. *Circulation*. 2003;107:139–146.

- Lahoud N, Abbas M-H, Salameh P, et al. A retrospective analysis of 254 acute stroke cases admitted to two university hospitals in Beirut: classification and associated factors. *Functional Neurology*. 2017;32(1):41-48.
- Lahoud N, Salameh P, Saleh N, et al. Prevalence of Lebanese stroke survivors: A comparative pilot study. *J Epidemiol Glob Health*. 2016;6(3):169-76.
- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises, part II: the aging heart in health: links to heart disease. *Circulation*. 2003;107:346–354.
- Lambiase MJ, Kubzansky LD, Thurston RC. Prospective study of anxiety and incident stroke. *Stroke*. 2014;45:438–443.
- Lanska DJ. Geographic distribution of stroke mortality in the United States: 1939–1941 to 1979–1981. *Neurology*. 1993;43:1839–1851.
- Larsson SC, Virtamo J, Wolk A. Total and specific fruit and vegetable consumption and risk of stroke: a prospective study. *Atherosclerosis*. 2013;227:147–152.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
- Lee BI, Nam HS, Heo JH, Kim DI Yonsei Stroke Team. Yonsei Stroke Registry. Analysis of 1,000 patients with acute cerebral infarctions. *Cerebrovasc Dis*. 2001;12:145–151. 47697.
- Lee M, Saver JL, Chang KH, et al. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341:c4249.
- Lee M, Saver JL, Hong KS, et al. Effect of pre-diabetes on future risk of stroke: meta-analysis. *BMJ*. 2012;344:e3564.
- Lee PN, Forey BA. Environmental tobacco smoke exposure and risk of stroke in nonsmokers: a review with meta-analysis. *J Stroke Cerebrovasc Dis*. 2006;15:190–201.
- Leng Y, Cappuccio FP, Wainwright NW, et al. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology*. 2015;84:1072–1079.
- Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002 Dec 14;360(9349):1903-13. Erratum in: *Lancet*. 2003 Mar 22;361(9362):1060.
- Li M, Hou WS, Zhang XW, et al. Obstructive sleep apnea and risk of stroke: a meta-analysis of prospective studies. *Int J Cardiol*. 2014;172:466–469.
- Li W, Wang D, Cao S, et al. Sleep duration and risk of stroke events and stroke mortality: a systematic review and meta-analysis of prospective cohort studies. *Int J Cardiol*. 2016;223:870–876.
- Liao D, Myers R, Hunt S, et al. Familial history of stroke and stroke risk: the Family Heart Study. *Stroke*. 1997;28:1908–1912.
- Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137:263–272.

Lip GY. Implications of the CHA(2)DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. *Am J Med.* 2011 Feb;124(2):111-4.

Lisabeth LD, Beiser AS, Brown DL, et al. Age at natural menopause and risk of ischemic stroke: the Framingham Heart Study. *Stroke.* 2009;40:1044–1049.

Lisabeth LD, Sánchez BN, Chervin RD, et al. High prevalence of poststroke sleep-disordered breathing in Mexican Americans. *Sleep Med.* 2017 May;33:97-102.

Loke YK, Brown JW, Kwok CS, et al. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* 2012;5:720–728.

Lopez-Espuela F, Zamorano JD, Ramírez-Moreno JM, et al. Determinants of Quality of Life in Stroke Survivors After 6 Months, from a Comprehensive Stroke Unit: A Longitudinal Study. *Biol Res Nurs.* 2015 Oct;17(5):461-8.

Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010 [published correction appears in *Lancet.* 2013;381:628] *Lancet.* 2012;380:2095–128.

Luengo-Fernandez R, Paul NL, Gray AM, et al. Oxford Vascular Study. Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford Vascular Study. *Stroke.* 2013;44:2854–2861.

Lykke JA, Langhoff-Roos J, Sibai BM, et al. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension.* 2009;53:944–951.

M

MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the Stroke Prevention in Young Women study. *Stroke.* 2007;38:2438–2445.

Mahmoodi BK, Yatsuya H, Matsushita K, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke.* 2014;45:1925–1931.

Malek AM, Cushman M, Lackland DT, et al. Secondhand smoke exposure and stroke: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Prev Med.* 2015;49:e89–e97.

Malik R, Traylor M, Pulit SL, et al. ISGC Analysis Group; METASTROKE collaboration; Wellcome Trust Case Control Consortium 2 (WTCCC2); NINDS Stroke Genetics Network (SiGN) Low-frequency and common genetic variation in ischemic stroke: the METASTROKE collaboration [published correction appears in *Neurology.* 2016;87:1306] *Neurology.* 2016;86:1217–1226.

Mancia G, Fagard R, Narkiewicz K, et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013 Jul;31(7):1281-357.

Martínez-García MA, Soler-Cataluña JJ, Ejarque-Martínez L, et al. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. *Am J Respir Crit Care Med.* 2009;180:36–41.

Martínez-González MA, Dominguez LJ, Delgado-Rodríguez M. Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. *Br J Nutr*. 2014;112:248–259.

Matar D, Frangieh AH, Abouassi S, et al. Prevalence, Awareness, Treatment, and Control of Hypertension in Lebanon. *J Clin Hypertens*. 2015; 17(5):381–8.

Mateen FJ, Carone M, Alam N, et al. A population-based case-control study of 1250 stroke deaths in rural Bangladesh. *Eur J Neurol* 2012;19:999–1006.

Mayhew AJ, de Souza RJ, Meyre D, et al. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br J Nutr*. 2016;115:212–225

McDonnell MN, Hillier SL, Hooker SP, et al. Physical activity frequency and risk of incident stroke in a national US study of blacks and whites. *Stroke*. 2013;44:2519–2524.

McKevitt C, Fudge N, Redfern J, et al. Self-reported long-term needs after stroke. *Stroke*. 2011 May;42(5):1398-403.

Meschia JF, Bushnell C, Boden-Albala B, et al. American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832.

Mohan KM, Wolfe CD, Rudd AG, et al (2011). Risk and Cumulative Risk of Stroke Recurrence: A Systematic Review and Meta-Analysis. *Stroke* 42:1489-1494.

Molshatzki N, Orion D, Tsabari R, et al. Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. *Cerebrovasc Dis*. 2011;31:271–277.

Morgenstern LB, Smith MA, Lisabeth LD, et al. Excess stroke in Mexican Americans compared with non-Hispanic whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 2004;160:376–383.

Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132.

Muir KW. The PREVAIL trial and low-molecular-weight heparin for prevention of venous thromboembolism. *Stroke*. 2008 Jul;39(7):2174-6.

Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study *Lancet*, 349 (1997), pp. 1269–1276.

N

Nakamura K, Barzi F, Lam TH, et al. Asia Pacific Cohort Studies Collaboration. Cigarette smoking, systolic blood pressure, and cardiovascular diseases in the Asia-Pacific region. *Stroke*. 2008;39:1694–1702.

National Center for Health Statistics. National Health Interview Survey. 2014 Public-use data file and documentation: NCHS tabulations. Available at: <http://www.cdc.gov/nchs/nhis/nhis_2014_data_release.htm>. NCHS tabulations. (Accessed on 10 July 2016)

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995 Dec 14;333(24):1581-7.

National Stroke Association, "Explaining Stroke 101". 2015. Available at: <https://www.stroke.org/sites/default/files/resources/Presentation_Explaining%20Stroke%20101.ppt> (Accessed on 01 February 2016)

Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet*. 2000 Dec 9;356(9246):1955-64.

Nedeltchev K, der Maur TA, Georgiadis D, et al. Ischaemic stroke in young adults: predictors of outcome and recurrence. *J Neurol Neurosurg Psychiatry*. 2005;76:191–195.

Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium the Stroke Genetics Network (SiGN) and the International Stroke Genetics Consortium (ISGC) Identification of additional risk loci for stroke and small vessel disease: a meta-analysis of genome-wide association studies. *Lancet Neurol*. 2016;15:695–707.

NHLBI. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 2000. Available at: <https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf> (Accessed on 12/08/2018)

NINDS Stroke Genetics Network (SiGN); International Stroke Genetics Consortium (ISGC) Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study [published correction appears in *Lancet Neurol*. 2016;15:241] *Lancet Neurol*. 2016;15:174–184.

Nishino Y, Tsuji I, Tanaka H, et al. Three-Prefecture Cohort Study Group. Stroke mortality associated with environmental tobacco smoke among never-smoking Japanese women: a prospective cohort study. *Prev Med*. 2014;67:41–45.

Nydevik I, Hulter-Asberg K. Subjective dysfunction after stroke. A study with Sickness Impact Profile. *Scand J Primary Health Care* 1992;9:271-5.

O

O'Donnell MJ, Xavier D, Liu L, et al. INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010 Jul 10;376(9735):112-23.

Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007 Oct;38(10):2633-9.

Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.

Olesen JB, Lip GY, Lane DA, et al. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med*. 2012 Aug. 125 (8):826.e13-23.

Oono IP, Mackay DF, Pell JP. Meta-analysis of the association between secondhand smoke exposure and stroke. *J Public Health (Oxf)* 2011;33:496–502.

Overvad TF, Nielsen PB, Larsen TB, et al. Left atrial size and risk of stroke in patients in sinus rhythm: a systematic review. *Thromb Haemost.* 2016;116:206–219.

Owolabi MO, Akarolo-Anthony S, Akinyemi R, et al. Members of the H3Africa Consortium. The burden of stroke in Africa: a glance at the present and a glimpse into the future. *Cardiovasc J Afr.* 2015 Mar-Apr;26(2) Suppl 1:S27–38.

Owolabi MO. Determinants of health-related quality of life in Nigerian stroke survivors. *Trans R Soc Trop Med Hyg.* 2008 Dec;102(12):1219-25.

P

Page RL, Wilkinson WE, Clair WK, et al. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation.* 1994;89:224–227.

Pan A, Sun Q, Okereke OI, et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review [published correction appears in *JAMA*. 2011;306:2565] *JAMA.* 2011;306:1241–1249.

Parra O, Arboix A, Montserrat JM, et al. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J.* 2004;24:267–272.

Perkovic V, Rodgers A. Redefining blood-pressure targets: SPRINT starts the marathon. *N Engl J Med.* 2015;373:2175–2178.

Perry HM, Roccella EJ. Conference report on stroke mortality in the southeastern United States. *Hypertension.* 1998;31:1206–1215.

Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet.* 2014;383:1973–1980.

Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke.* 2013;44:2821–2828.

Pezzini A, Grassi M, Lodigiani C, et al on behalf of the Italian Project on Stroke in Young Adults (IPSYA) Investigators. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian Project on Stroke in Young Adults. *Circulation.* 2014;129:1668–1676.

Pezzini A, Grassi M, Lodigiani C, et al. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian Project on Stroke in Young Adults. *Circulation.* 2014;129:1668–1676.

Pickard S, Johnson JA, Penn A, et al. Replicability of SF-36 summary scores by the SF-12 in stroke patients. *Stroke* 1999;30:1213-7.

Pisters Ron, Lane DA, Nieuwlaat R, et al. A Novel User-Friendly Score (HAS-BLED) to Assess 1-Year Risk of Major Bleeding in Patients with Atrial Fibrillation. *Chest.* 2010. 138 (5): 1093–100.

Poirier P, Giles TD, Bray GA, et al. American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2006;113:898–918.

Poli D, Antonucci E, Grifoni E, et al. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost*. 2009;101:938–942.

Poungvarin N, Bhoopat W, Viriyavejakul A, et al. Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. *N Engl J Med*. 1987;316:1229–1233.

Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018 Mar;49(3):e46-e110. Erratum in: *Stroke*. 2018 Mar;49(3):e138. *Stroke*. 2018 Apr 18.

Powers WJ, Rabinstein AA, Ackerson T, et al. American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018 Mar;49(3):e46-e110.

Prospective Studies Collaboration. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths [published correction appears in *Lancet*. 2008;372:292] *Lancet*. 2007;370:1829–1839.

Psaty BM, Anderson M, Kronmal RA, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2004;52:1639–1647.

R

Redfors P, Jood K, Holmegaard L, et al. Stroke subtype predicts outcome in young and middle-aged stroke sufferers. *Acta Neurol Scand*. 2012;126:329–335.

Renoux C, Dell’aniello S, Garbe E, et al. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ*. 2010;340:c2519.

Riachy M, Sfeir F, Sleilaty G, et al. Prediction of the survival and functional ability of severe stroke patients after ICU therapeutic intervention. *BMC Neurology*. 2008;8:24.

Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev*. 2015;(8):CD011054.

Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. 2012 Jan 3;125(1):e2-e220. Erratum in: *Circulation*. 2012 Jun 5;125(22):e1002. et al. Heart Disease and Stroke Statistics—2012 Update: A Report From the American Heart Association. *Circulation*, 2012, 125:e2-e220

Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women’s Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.

Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford vascular study). *Lancet* 2005;366:1773-83.

Rowat A, Graham C, Dennis M. Renal dysfunction in stroke patients: a hospital-based cohort study and systematic review. *Int J Stroke*. 2014;9:633–639.

Royal College of Physicians Sentinel Stroke National Audit Programme (SSNAP). National clinical audit annual results portfolio March 2015-April 2016. Available at: <<http://bit.ly/1M5R3Op>> (Accessed 26 October 2016).

Ruehland WR, Rochford PD, O'Donoghue FJ, et al. The New AASM Criteria for Scoring Hypopneas: Impact on the Apnea Hypopnea Index. *Sleep*. 2009;32(2):150-157.

Russo T, Felzani G, Marini C. Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. *J Aging Res*. 2011;2011:108785.

Rutten-Jacobs LC, Maaijwee NA, Arntz RM, et al. Long-term risk of recurrent vascular events after young stroke: the FUTURE study. *Ann Neurol*. 2013;74:592–601.

S

Sacco S, Marini C, Totaro R, et al. A population-based study of the incidence and prognosis of lacunar stroke. *Neurology*. 2006 May 9. 66(9):1335-8.

Sahlin C, Sandberg O, Gustafson Y, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. *Arch Intern Med*. 2008;168:297–301.

Saladin LK. Measuring quality of life post-stroke. *Neurology Report* 2000;24:133-9.

Salameh P, Farah R, Hallit S, et al. *Environ Monit Assess*. 2018;190:153.

Sandsmark DK, Messé SR, Zhang X, et al. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic Renal Insufficiency Cohort Study. *Stroke*. 2015;46:2075–2080.

Schürks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009;339:b3914.

Seshadri S, Beiser A, Pikula A, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. *Circulation*. 2010 Mar 23; 121(11):1304–12.

Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917–932.

Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2003;34:623–631.

Shi ZQ, Tang JJ, Wu H, et al. Consumption of nuts and legumes and risk of stroke: a meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis*. 2014;24:1262–1271.

Shou J, Zhou L, Zhu S, et al. Diabetes is an independent risk factor for stroke recurrence in stroke patients: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2015;24:1961–1968.

Sibai A, Hwalla N. WHO STEPS-Chronic disease risk factor surveillance: data book for Lebanon [Internet]. Available from: <http://www.who.int/chp/steps/2008_STEPS_Lebanon.pdf> (Accessed on 2015 May 22)

Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS) *Circulation*. 2001;103:638–642.

Sousa RM, Ferri CP, Acosta D, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. *Lancet* 2009;374:1821-1830.

SPS3 Study Group. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial [published correction appears in *Lancet*. 2013;382:506] *Lancet*. 2013;382:507–515.

Strickberger SA, Ip J, Saksena S, et al. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm*. 2005;2:125–131.

Stroke Association. State of the nation. Stroke statistics. 2017. Available at: <https://www.stroke.org.uk/sites/default/files/state_of_the_nation_2017_final_1.pdf> (Accessed on 13 August 2018)

Stroke Foundation. Stroke risk info. available at: <<https://strokefoundation.org.au>> Accessed on 27/07/2018

Stroke Prevention Atrial Fibrillation III Writing Committee. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. *JAMA*. 1998 Apr 22-29. 279(16):1273-7.

Sturgeon JD, Folsom AR, Longstreth WT, et al. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke*. 2007;38:2718–2725.

Suk SH, Sacco RL, Boden-Albala B, et al. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke* 2003; 34:1586 –1592.

T

Tayal AH, Tian M, Kelly KM, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology*. 2008;71:1696–1701.

The internet stroke center. Stroke statistics. Available at: <<http://www.strokecenter.org/patients/about-stroke/stroke-statistics/>> (Accessed on 27 August 2018)

Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. Hacke W, Kaste M, Bluhmki E, et al. *N Engl J Med*. 2008 Sep 25; 359(13):1317-29

Tikk K, Sookthai D, Monni S, et al. Primary preventive potential for stroke by avoidance of major lifestyle risk factors: the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort. *Stroke*. 2014;45:2041–2046.

Tirschwell DL, Smith NL, Heckbert SR, et al. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. *Neurology*. 2004;63:1868–1875.

Tohme RA, Jurjus AR, Estephan A. The prevalence of hypertension and its association with other cardiovascular disease risk factors in a representative sample of the Lebanese population. *J Hum Hypertens*. 2005; 19(11):861–8.

Towfighi A, Markovic D, Ovbiagele B. Current national patterns of comorbid diabetes among acute ischemic stroke patients. *Cerebrovasc Dis*. 2012;33:411–418.

Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies [published correction appears in *Lancet Neurol.* 2015;14:788] *Lancet Neurol.* 2012;11:951–962.

Traylor M, Mäkelä KM, Kilarski LL, et al. A novel MMP12 locus is associated with large artery atherosclerotic stroke using a genome-wide age-at-onset informed approach. *PLoS Genet.* 2014;10:e1004469.

Traylor M, Rutten-Jacobs LC, Holliday EG, et al. Differences in common genetic predisposition to ischemic stroke by age and sex. *Stroke.* 2015;46:3042–3047.

Truelsen T, Begg S, Mathers C. The global burden of cerebrovascular disease. 2000. Available at: <http://www.who.int/healthinfo/statistics/bod_cerebrovascularstroke.pdf> (Accessed on 13 August 2018)

Turakhia MP, Ziegler PD, Schmitt SK, et al. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. *Circ Arrhythm Electrophysiol.* 2015;8:1040–1047.

Turkington PM, Bamford J, Wanklyn P, et al. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. *Stroke.* 2002;33:2037–2042.

U

US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310:591–608.

V

van der Lee JH, Wagenaar RC, Lankhorst GJ, et al. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. *Stroke* 1999;30:2369-75.

van Straten A, de Haan RJ, Limburg M et al. A stroke-adapted 30-item version of the Sickness Impact Profile to assess quality of life (SA-SIP30). *Stroke.* 1997 Nov;28(11):2155-61.

van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke.* 2009 Apr. 40 (4):1410-6.

Vincent C, Desrosiers J, Landreville P, et al. Burden of caregivers of people with stroke: evolution and predictors. *Cerebrovasc Dis.* 2009; 27(5):456-64.

Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med.* 2001;345:1243–1249.

Vital Signs: Recent trends in stroke death rates – United States, 2000–2015. *MMWR* 2017;66.

W

Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA.* 2003;290:1049–1056.

- Wang X, Dong Y, Qi X, et al. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke*. 2013;44:1833–1839.
- Wang Y, Rudd AG, Wolfe CD. Age and ethnic disparities in incidence of stroke over time: the South London Stroke Register. *Stroke* 2013;44:3298-3304.
- Wang ZM, Zhao D, Nie ZL, et al. Flavonol intake and stroke risk: a meta-analysis of cohort studies. *Nutrition*. 2014;30:518–523.
- Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet*. 2012;379(9834):2364–2372.
- Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet*. 2012;379(9834):2364-2372.
- Ware JE, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: construction of scales and preliminary test of reliability and validity. *MedCare* 1996;34:220-6.
- Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women’s Health Initiative: a randomized trial. *JAMA*. 2003;289:2673–2684.
- White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 2005; 111:1327-31.
- WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* (London, England) 1996;348:498–505.
- WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:505–510.
- WHO. Lebanon. WHO. Available from: <<http://www.who.int/countries/lbn/en/>> (Accessed on 26 May 2015).
- WHO MONICA Project Investigators. The World Health Organization MONICA Project (Monitoring trends and determinants in cardiovascular disease). *J Clin Epidemiol* 41, 105-114. 1988.
- WHO. Disability-adjusted life years (DALYs) Available at: <http://www.who.int/gho/mortality_burden_disease/daly_rates/text/en/> (Accessed on 27 August 2018)
- Wieberdink RG, Poels MM, Vernooij MW, et al. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 2011;31:2982–2989.
- Willey JZ, Moon YP, Paik MC, et al. Physical activity and risk of ischemic stroke in the Northern Manhattan Study. *Neurology*. 2009;73:1774–1779.
- Willey JZ, Moon YP, Sacco RL, et al. Physical inactivity is a strong risk factor for stroke in the oldest old: findings from a multi-ethnic population (the Northern Manhattan Study). *Int J Stroke*. 2017;12:197–200.

Williams FM, Carter AM, Hysi PG, et al. Ischemic stroke is associated with the ABO locus: the EuroCLOT study [published correction appears in *Ann Neurol*. 2014;75:166–167] *Ann Neurol*. 2013;73:16–31.

Williams LS, Weinberger M, Harris LE, et al. Development of a stroke-specific quality of life scale. *Stroke* 1999;30:1362-9.

Williams LS, Weinberger M, Harris LE, et al. Measuring quality of life in a way that is meaningful to stroke patients. *Neurology* 1999;53:1839-43.

Williams S. Health related quality of life outcomes in outcomes in strokes. *Neuroepidemiology* 1998;17:116-20.

Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.

Woo D, Falcone GJ, Devan WJ, et al. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet*. 2014;94:511–521.

Woo D, Gebel J, Miller R, et al. Incidence rates of first-ever ischemic stroke subtypes among blacks: a population-based study. *Stroke*, 1999, 30:2517-22.

World Health Organisation (WHO). The top 10 causes of death. 24 May 2018 Available at: <<http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>> (Accessed on 27 August 2018)

World Health Organisation. (2014). The top 10 causes of death. Available at: <<http://bit.ly/1c9a3vO>> (Accessed 20 December 2016).

World Health Organization. The top 10 causes of death. 2014. Available at: <<http://who.int/mediacentre/factsheets/fs310/en/>> (Accessed 19 October 2016).

World Heart Federation (WHF), Stroke. 2017. Available at: <<http://www.world-heart-federation.org/cardiovascular-health/stroke/>> (Accessed on 01 May 2017)

WRITING GROUP MEMBERS, Benjamin EJ, Blaha MJ, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135(10):e146-e603.

Wu CM, McLaughlin K, Lorenzetti DL, et al. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:2417–2422.

Wu D, Guan Y, Lv S, et al. No evidence of increased risk of stroke with consumption of refined grains: a meta-analysis of prospective cohort studies. *J Stroke Cerebrovasc Dis*. 2015;24:2738–2746.

Wyller TB, Holmen J, Laake P, et al. Correlates of subjective well-being in stroke patients. *Stroke* 1998;29:363-7.

X

Xu Z, Li Y, Tang S, et al. Current use of oral contraceptives and the risk of first-ever ischemic stroke: A meta-analysis of observational studies. *Thromb Res* 2015; 136:52-60.

Z

Zhang Y, Chapman AM, Plested M, et al. The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. *Stroke Res Treat* 2012; 2012: 436125

Zhang Y, Tuomilehto J, Jousilahti P, et al. Lifestyle factors and antihypertensive treatment on the risks of ischemic and hemorrhagic stroke. *Hypertension*. 2012 Oct; 60(4):906–12.

Zhang Y, Tuomilehto J, Jousilahti P, et al. Total and high-density lipoprotein cholesterol and stroke risk. *Stroke*. 2012;43:1768–1774.

APPENDIX

Appendix 1: Stroke definitions

Table 1. Definition of Stroke

The term “stroke” should be broadly used to include all of the following:

Definition of CNS infarction: CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on

1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes hemorrhagic infarctions, types I and II; see “Hemorrhagic Infarction.”)

Definition of ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. (Note: Evidence of CNS infarction is defined above.)

Definition of silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Definition of intracerebral hemorrhage: A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

(Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types I and II—see “Hemorrhagic Infarction.”)

Definition of stroke caused by intracerebral hemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Definition of silent cerebral hemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.

Definition of subarachnoid hemorrhage: Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).

Definition of stroke caused by subarachnoid hemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Definition of stroke caused by cerebral venous thrombosis: Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

Definition of stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above.

CNS indicates central nervous system.

Appendix 2: NIH Stroke Scale

Instructions	Scale Definition	Score
<p>1a. Level of Consciousness The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/ bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p>0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.</p>	<p>_____</p>
<p>1b. LOC Questions The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.</p>	<p>0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.</p>	<p>_____</p>
<p>1c. LOC Commands The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.</p>	<p>0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.</p>	<p>_____</p>

Instructions	Scale Definition	Score
<p>2. Best Gaze Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve palsy (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</p>	<p>0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.</p>	<p>_____</p>
<p>3. Visual Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve palsy (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</p>	<p>0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).</p>	<p>_____</p>
<p>4. Facial Palsy Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).</p>	<p>_____</p>

Instructions	Scale Definition	Score
<p>5. Motor Arm</p> <p>The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds.</p> <p>1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.</p> <p>2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.</p> <p>3 = No effort against gravity; limb falls.</p> <p>4 = No movement.</p> <p>UN = Amputation or joint fusion, explain:</p> <p>_____</p> <p>5a. Left Arm</p> <p>5b. Right Arm</p>	<p>_____</p> <p>_____</p>
<p>6. Motor Leg</p> <p>The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 = No drift; leg holds 30-degree position for full 5 seconds.</p> <p>1 = Drift; leg falls by the end of the 5-second period but does not hit bed.</p> <p>2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.</p> <p>3 = No effort against gravity; leg falls to bed immediately.</p> <p>4 = No movement.</p> <p>UN = Amputation or joint fusion, explain:</p> <p>_____</p> <p>_____</p> <p>6a. Left Leg</p> <p>6b. Right Leg</p>	<p>_____</p> <p>_____</p>

Instructions	Scale Definition	Score
<p>7. Limb Ataxia</p> <p>This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</p>	<p>0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain:</p> <hr/> <hr/>	<hr/>
<p>8. Sensory</p> <p>Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.</p>	<p>0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.</p>	<hr/>

Instructions	Scale Definition	Score
<p>9. Best Language</p> <p>A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences.</p> <p>Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</p>	<p>0 = No aphasia; normal.</p> <p>1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.</p> <p>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.</p> <p>3 = Mute, global aphasia; no usable speech or auditory comprehension.</p>	<p>_____</p>
<p>10. Dysarthria</p> <p>If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</p>	<p>0 = Normal.</p> <p>1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.</p> <p>2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</p> <p>UN = Intubated or other physical barrier, explain: _____</p>	<p>_____</p>

Instructions	Scale Definition	Score
<p>11. Extinction and Inattention (formerly Neglect)</p> <p>Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = No abnormality.</p> <p>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</p>	<p>_____</p>

Appendix 3: SF-36 questionnaire

Name: _____
ID#: _____

Ref. Dr: _____
Age: _____

Date: _____
Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

Excellent Very Good Good Fair Poor

Compared to one year ago, how would you rate your health in general now?

- Much better now than one year ago
- Somewhat better now than one year ago
- About the same
- Somewhat worse now than one year ago
- Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Were limited in the kind of work or other activities

Yes No

Had difficulty performing the work or other activities (for example, it took extra effort)

Yes No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Didn't do work or other activities as carefully as usual

Yes No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all Slightly Moderately Severe Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

None Very Mild Mild Moderate Severe Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time

- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

- Definitely true Mostly true Don't know Mostly false Definitely false

I am as healthy as anybody I know

- Definitely true Mostly true Don't know Mostly false Definitely false

I expect my health to get worse

- Definitely true Mostly true Don't know Mostly false Definitely false

My health is excellent

- Definitely true Mostly true Don't know Mostly false Definitely false

Appendix 4: Stroke Specific Quality of Life Scale (SS-QOL) questionnaire

Scoring: each item shall be scored with the following key

Total help - Couldn't do it at all - Strongly agree	1
A lot of help - A lot of trouble - Moderately agree	2
Some help - Some trouble - Neither agree nor disagree	3
A little help - A little trouble - Moderately disagree	4
No help needed - No trouble at all - Strongly disagree	5

Energy

1. I felt tired most of the time. _____
2. I had to stop and rest during the day. _____
3. I was too tired to do what I wanted to do. _____

Family Roles

1. I didn't join in activities just for fun with my family. _____
2. I felt I was a burden to my family. _____
3. My physical condition interfered with my personal life. _____

Language

1. Did you have trouble speaking? For example, get stuck, stutter, stammer, or slur your words? _____
2. Did you have trouble speaking clearly enough to use the telephone? _____
3. Did other people have trouble in understanding what you said? _____
4. Did you have trouble finding the word you wanted to say? _____
5. Did you have to repeat yourself so others could understand you? _____

Mobility

1. Did you have trouble walking? (If patient can't walk, go to question 4 and score questions 2-3 as 1.) _____
2. Did you lose your balance when bending over to or reaching for something? _____
3. Did you have trouble climbing stairs? _____
4. Did you have to stop and rest more than you would like when walking or using a wheelchair? _____
5. Did you have trouble with standing? _____
6. Did you have trouble getting out of a chair? _____

Mood

1. I was discouraged about my future. _____
2. I wasn't interested in other people or activities. _____
3. I felt withdrawn from other people. _____
4. I had little confidence in myself. _____
5. I was not interested in food. _____

Personality

1. I was irritable. _____
2. I was impatient with others. _____
3. My personality has changed. _____

Self Care

1. Did you need help preparing food? _____
2. Did you need help eating? For example, cutting food or preparing food? _____
3. Did you need help getting dressed? For example, putting on socks or shoes, buttoning buttons, or zipping? _____
4. Did you need help taking a bath or a shower? _____

5. Did you need help to use the toilet? _____

Social Roles

1. I didn't go out as often as I would like. _____

2. I did my hobbies and recreation for shorter periods of time than I would like. _____

3. I didn't see as many of my friends as I would like. _____

4. I had sex less often than I would like. _____

5. My physical condition interfered with my social life. _____

Thinking

1. It was hard for me to concentrate. _____

2. I had trouble remembering things. _____

3. I had to write things down to remember them. _____

Upper Extremity Function

1. Did you have trouble writing or typing? _____

2. Did you have trouble putting on socks? _____

3. Did you have trouble buttoning buttons? _____

4. Did you have trouble zipping a zipper? _____

5. Did you have trouble opening a jar? _____

Vision

1. Did you have trouble seeing the television well enough to enjoy a show? _____

2. Did you have trouble reaching things because of poor eyesight? _____

3. Did you have trouble seeing things off to one side? _____

Work/Productivity

1. Did you have trouble doing daily work around the house? _____

2. Did you have trouble finishing jobs that you started? _____

3. Did you have trouble doing the work you used to do? _____

TOTAL SCORE _____

Appendix 5: Geriatric Depression Scale (Short Form) questionnaire

Patient's Name:

Date:

Instructions:

Choose the best answer for how you felt over the past week. Note: when asking the patient to complete the form, provide the self-rated form (included on the following page).

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	YES / <i>NO</i>	
2.	Have you dropped many of your activities and interests?	<i>YES</i> / NO	
3.	Do you feel that your life is empty?	<i>YES</i> / NO	
4.	Do you often get bored?	<i>YES</i> / NO	
5.	Are you in good spirits most of the time?	YES / <i>NO</i>	
6.	Are you afraid that something bad is going to happen to you?	<i>YES</i> / NO	
7.	Do you feel happy most of the time?	YES / <i>NO</i>	
8.	Do you often feel helpless?	<i>YES</i> / NO	
9.	Do you prefer to stay at home, rather than going out and doing new things?	<i>YES</i> / NO	
10.	Do you feel you have more problems with memory than most people?	<i>YES</i> / NO	
11.	Do you think it is wonderful to be alive?	YES / <i>NO</i>	
12.	Do you feel pretty worthless the way you are now?	<i>YES</i> / NO	
13.	Do you feel full of energy?	YES / <i>NO</i>	
14.	Do you feel that your situation is hopeless?	<i>YES</i> / NO	
15.	Do you think that most people are better off than you are?	<i>YES</i> / NO	
		TOTAL	

(Sheikh & Yesavage, 1986)

Scoring:

Answers indicating depression are in bold and italicized; score one point for each one selected. A score of 0 to 5 is normal. A score greater than 5 suggests depression.

Sources:

- Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol. 1986 June;5(1/2):165-173.
- Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull. 1988;24(4):709-711.
- Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-83;17(1):37-49.

Hospital Name: _____	File number: _____
ID number: _____	

PERSONAL INFORMATION

Name: _____ Father name: _____

SEX: M F DATE OF BIRTH: |__|__|____|

Address: _____ Province: _____

Telephone: _____ Cell phone: _____

Third party payer: NSFF MOPH Military Gov (COOP)† Gov (ISF)
 Private Insurance† † Out of pocket Other: _____
(multiple choices possible) †

Weight : _____ Kg Height: _____ cm

Marital status: Single Married Divorced Widowed

Housing situation:

- Alone
- With family
- In an institution, specify: _____
- Other, specify: _____

Education:

- Illiterate
- Elementary school
- Secondary school
- High school
- University

Professional conditions:

- Employed
- Student
- Housewife*
- Retired
- Unemployed

If the patient has a job, specify activity:

- EMPLOYED
- Worker
- Employed
- Executive, manager, director
- Other

- SELF EMPLOYED
- Entrepreneur
- Freelancer
- Other

** In category "housewife" includes all patients who actually carry out domestic activities.*

Monthly personal income: < 750.000 L.L. [750-1.500.000] LL
 [1.500.000–2.250.000] LL > 2.250.000 LL

PAST MEDICAL HISTORY

Pathology	Details
<input type="checkbox"/> Hypertension	<u>Therapy:</u> <input type="checkbox"/> None <input type="checkbox"/> Diet <input type="checkbox"/> Diuretic <input type="checkbox"/> B-blocker <input type="checkbox"/> Ca-antagonist <input type="checkbox"/> ACE Inhibitor <input type="checkbox"/> Angiotensin II receptor blockers (ARB)
<input type="checkbox"/> Atrial Fibrillation	<input type="checkbox"/> Permanente <input type="checkbox"/> Paroxysmal <u>Therapy:</u> <input type="checkbox"/> None <input type="checkbox"/> Anti-platelet <input type="checkbox"/> Oral Anticoagulants <input type="checkbox"/> _____ INR: <input type="checkbox"/> <2.0; <input type="checkbox"/> 2.0-3.0; <input type="checkbox"/> > 3.0
<input type="checkbox"/> Hyperlipidemia	<input type="checkbox"/> Total cholesterol > 200 mg/dL Indicate triglycerides value _____ Drug treatment: <input type="checkbox"/> No <input type="checkbox"/> Yes, specify them: _____
<input type="checkbox"/> Reduced glucose tolerance	<input type="checkbox"/> Fasting glucose > 126 mg/dL
<input type="checkbox"/> Diabetes Mellitus	<input type="checkbox"/> IDDM <input type="checkbox"/> NIDDM
<input type="checkbox"/> Previous stroke	Number _____ 1st year of stroke: _____
<input type="checkbox"/> Previous TIA	Number _____ 1st year of TIA: _____
<input type="checkbox"/> Previous MI	Number _____ 1st year of MI: _____
<input type="checkbox"/> Other, specify: _____	<u>Therapy:</u> _____
<input type="checkbox"/> Other, specify: _____	<u>Therapy:</u> _____
<input type="checkbox"/> Other, specify: _____	<u>Therapy:</u> _____

Is the patient a smoker? No Yes Ex-smoker

Was the patient previously subjected to surgery? No Yes If yes, specify which:

LEVEL OF DISABILITY AT ADMISSION

1. Barthel Index

(Fill the scale with respect to the patient's ability before the stroke)

Date of completion of the scale: ____ / ____ / ____
dd mm yy

NOT DETERMINED

Activity	Score
FEEDING	
0 = unable	
5 = needs help cutting, spreading butter, etc., or requires modified diet	
10 = independent	_____
BATHING	
0 = dependent	
5 = independent (or in shower)	_____
GROOMING	
0 = needs to help with personal care	
5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING	
0 = dependent	
5 = needs help but can do about half unaided	
10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS	
0 = incontinent (or needs to be given enemas)	
5 = occasional accident	
10 = continent	_____
BLADDER	
0 = incontinent, or catheterized and unable to manage alone	
5 = occasional accident	
10 = continent	_____
TOILET USE	
0 = dependent	
5 = needs some help, but can do something alone	
10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK)	
0 = unable, no sitting balance	
5 = major help (one or two people, physical), can sit	
10 = minor help (verbal or physical)	
15 = independent	_____
MOBILITY (ON LEVEL SURFACES)	
0 = immobile or < 46 meters	
5 = wheelchair independent, including corners, > 46 meters	
10 = walks with help of one person (verbal or physical) , > 46 meters	
15 = independent (but may use any aid; for example, stick), > 46 meters	_____

Instructions	Scale Definition	Score
4. Facial Palsy	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm	0 = No drift ; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift ; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity ; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity ; limb falls. 4 = No movement . UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm	_____ _____
6. Motor Leg	0 = No drift ; leg holds 30-degree position for full 5 seconds. 1 = Drift ; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity ; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity ; leg falls to bed immediately. 4 = No movement . UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg	_____ _____
7. Limb Ataxia	0 = Absent . 1 = Present in one limb . 2 = Present in two limbs . UN = Amputation or joint fusion, explain: _____	_____
8. Sensory	0 = Normal ; no sensory loss. 1 = Mild-to-moderate sensory loss ; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss ; patient is not aware of being touched in the face, arm, and leg.	_____

Instructions	Scale Definition	Score
<p>9. Best Language</p>	<p>0 = No aphasia; normal.</p> <p>1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.</p> <p>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.</p> <p>3 = Mute, global aphasia; no usable speech or auditory comprehension.</p>	<p>_____</p>
<p>10. Dysarthria</p>	<p>0 = Normal.</p> <p>1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.</p> <p>2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</p> <p>UN = Intubated or other physical barrier, explain: _____</p>	<p>_____</p>
<p>11. Extinction and Inattention (formerly Neglect)</p>	<p>0 = No abnormality.</p> <p>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</p>	<p>_____</p>

HOSPITALIZATION DATA

During the hospitalization, was the patient submitted to instrumental diagnostic tests due to stroke?

No Yes, If Yes, specify:

Type	Number	Expenditure
Brain computed tomography (CT) including that of diagnosis		
Brain computed tomography with contrast		
Brain imaging (MRI)		
Supra-aortic Doppler		
Transcranial Doppler		
Cerebral angiography		
Magnetic resonance angiography (MRA)		
Electro-cardiogram		
Dynamic electro-cardiogram type Holter (24 hours)		
Transthoracic echocardiogram		
Transesophageal echocardiogram		
Electro-encephalogram		
Chest X-ray		
Neuropsychological evaluation (cognitive, language disorders, etc.)		
Other, specify:		
Other, specify:		
Other, specify:		
Other, specify:		
Other, specify:		
Other, specify:		

During the hospitalization, was the patient submitted to laboratory tests due to stroke?

No Yes, If Yes, specify:

Type	Number	Expenditure
Glycemia		
HbA1c		
INR		
T. Quick (TP)		
Activated Partial Thromboplastin Time		
Fibrinogen		
Platelet aggregation		
BUN		
Creatinine		
Blood count		
SGOT		
SGPT		
GGT		
Alkaline phosphatase		
LDH		
Bilirubin		
CPK		
ESR (erythrocyte sedimentation rate)		
APC (activated protein C) PCR		

Type	Number	Expenditure
Blood Gas Total cholesterol Triglycerides Urine analysis (specify if with culture) ANA Other specify: Other specify: Other specify: Other specify: Other specify:		

During the hospitalization, was the patient referred to a rehabilitation therapy specialist because of stroke?

- No Yes, If Yes, specify:

Type of therapy	Therapy initiation date	No. of overall sessions	Expenditure
Physical rehabilitation			
Occupational therapy			
Speech therapy			

During the hospitalization, was the patient visited by a specialist due to stroke?

- No Yes, If Yes, please specify:

Visit type	Number	Expenditure

During the hospitalization, did the patient receive any drug therapy?

- No Yes, If Yes, please specify:

Molecule	Dose and frequency (daily/weekly etc.) (tablets, ampoule, drops, etc.)	Duration of treatment (days)	Correlation with stroke (Yes/No)	The patient was taking it the previous stroke (Yes/No)	Expenditure

During the hospitalization, was it necessary to do these actions because of stroke:

- Percutaneous Endoscopic Gastrostomy number of days _____ cost per day _____
- Nasogastric tube number of days _____ cost per day _____
- Catheter number of days _____ cost per day _____
- Parenteral nutrition number of days _____ cost per day _____
- Elastic stocking number of days _____ cost per day _____
- Monitoring vital functions number of hours _____ cost per hour _____
- _____ _____ cost per day/h _____
- _____ _____ cost per day/h _____

During the hospitalization, has critical events occurred (ex. infarction, fractures, heart failure, bronchopneumonia etc.) because of stroke that have required additional health services?

- No Yes, If Yes, specify:

Event Description	Health Service	Expenditure

During hospitalization, was the patient submitted to surgery?

- No Yes, If Yes, please specify:
- Neurosurgery
 - Carotid surgery
 - Vascular surgery, specify _____
 - Another surgery, specify _____
 - Number of hour using the operating room: _____

In the scope of the same hospital, was the patient transferred to another division/ward of the same hospital (even the return of the patient to the department/ward he was first admitted to is considered a transfer)?

- No Yes, If Yes, please specify:

Transfer	Date of transfer	From (Ward)	To (Ward)
1st Transfer			
2nd Transfer			
3rd Transfer			
4th Transfer			

HOSPITAL DISCHARGE DATA

The patient was admitted in: _____ division/ward

Total days the patient spent in the division/ward: _____

Discharge date: ____ / ____ / ____
 dd mm yy

Drug therapy at discharge:

MOLECULE	DOSE AND FREQUENCY (ex. DAILY / WEEKLY) (tablets, ampoule, drops)	DURATION OF TREATMENT (DAYS)

Neurological diagnosis:

- Hemorrhagic stroke: in typical site in atypical site
- Ischemic stroke (TOAST criteria, 1993)
 - Atherosclerosis of vessels of large caliber
 - Cardioembolic (possible / likely)
 - Occlusion of small vessels
 - Stroke by different causes
 - Stroke from causes not certain:
 - a. identification of two or more causes
 - b. negative evaluation
 - c. incomplete evaluation

How to discharge the patient from the hospital in which he was admitted:

- Ordinary to the patient's home
- Transfer directly to another institution of hospitalization and treatment, public or private (in the case of direct transfer, arranged by the hospital).
 Indicate name of the institution: _____
- Death of the patient on --/--/----
- Discharge ordinary at a nursing home
- Discharge to the patient's home with home hospitalization
- Transfer to another type or system of hospitalization (day hospital - rehabilitation or long-term care), inside the institution
- Transfer to another public or private institution to begin a rehabilitation therapy.
 Indicate name of the institution: _____
- Discharge ordinary with an integrated home care (nursing care at home)

TRANSFERS (BED TO CHAIR AND BACK)

- 0 = unable, no sitting balance
- 5 = major help (one or two people, physical), can sit
- 10 = minor help (verbal or physical)
- 15 = independent _____

MOBILITY (ON LEVEL SURFACES)

- 0 = immobile or < 46 meters
- 5 = wheelchair independent, including corners, > 46 meters
- 10 = walks with help of one person (verbal or physical) , > 46 meters
- 15 = independent (but may use any aid; for example, stick), > 46 meters _____

STAIRS

- 0 = unable
- 5 = needs help (verbal, physical, carrying aid)
- 10 = independent _____

TOTAL (0-100): _____

2. Modified Rankin Scale

DATE OF COMPLETION OF SCALE: ____ / ____ / ____
dd mm yy

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0-6): _____

Appendix 7: Submitted article

Submissions Being Processed for Author **Rachel Raymond Abdo, PharmD, MPH, PhD first year student**

Page: 1 of 1 (1 total submissions) Display results per page.

Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status
View Submission Send E-mail	JSCVD-D-18-01080	Mortality and predictors of death post stroke: Data from a multicenter prospective cohort of Lebanese stroke patients	Aug 31, 2018	Sep 02, 2018	Under Review

Page: 1 of 1 (1 total submissions) Display results per page.

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