"ASSESSMENT OF DRUG UTILISATION PATTERN FOR STROKE PATIENTS IN TERTIARY CARE HOSPITAL"

Sankha Shubra Saha[1], Nivedita Patel[1], Vidit Patel[1], Zainab Lokhanwala[1], Harsh P Patel[1], Parthkumar Janakbhai Panchal[1], Prashant Vaghela[1], Jagdish Kakadiya[2*], Gunosindhu Chakraborthy[3]

[1]Dept. of Pharm d scholar, Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujarat
[2]Professor, Dept. of Pharmacology Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujara
[3]Professor and Principal, Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujarat
Corresponding Author: Email Id: jagdishbhai.kakadiya@paruluniversity.ac.in

KEYWORDS
Stroke, drug utilisation pattern, management

ABSTRACT

BACKGROUND: Stroke represents a major public health concern globally, with significant implications for both patients and healthcare systems. The appropriate use of medications is essential in managing strokes to lower the risk of serious disease and demise. Pharmacotherapy plays a central role in the acute and long-term management of stroke, encompassing a range of medications aimed at preventing recurrence, managing risk factors, and promoting recovery.

OBJECTIVE: Evaluating the pattern of drug usage in stroke patients admitted to a specialized referral hospital**.**

MATERIALS AND METHODS: In this study data of the patients receiving treatment of stroke is obtained. Total 154 patients' data was collected and observed from Parul sevashram hospital. In the data collection analysis form, the data was reported and analysed using graphical representations and is summarized.

RESULT: In 154 patients the common medications like enoxaparin, heparin, aspirin, clopidogrel were used. Various classes of antihypertensive drugs were prescribed for 53 hypertensive patients, while phenytoin was administered to those with seizures. Atorvastatin and mannitol were also frequently prescribed. Antibiotics, lactulose, andcerebral activators like citicholine were utilized to address specific needs.

CONCLUSION: The study concluded that males are more prone to stroke and patients with age of 46-60 years have more common occurrence for stroke with risk factor of hypertension and high cholesterol levels. Atorvastatin,aspirin and clopidogrel is the usually prescribed drug in the study. To promote safe and efficientdrug use, the selection of drugs should be focused.

INTRODUCTION:

Stroke which is also known as Cerebral Artery Blockage mainly occurs due to the shortage of oxygen, as a result brain cells quickly perish leading to disruption in blood flow[1]. Haemorrhagic and ischemic strokes are the two main categories of strokes. Both thrombotic and embolic events can result from ischemic blockage of the brain[2]. Narrowing of blood vessels due to atherosclerosis restricts blood flow, leading to thrombosis. As plaque builds up, the vessel's diameter decreases, increasing the likelihood of clot formation and ultimately causing a thrombotic stroke. Necrosis results in the breakdown of the cell's outer membrane, organelles enlarging and spilling their contents into the extracellular space[3],and ultimately,

neuronal death. Roughly 10-15% of all strokes are haemorrhagic strokes, which have a high death rate. In this condition, blood vessels rupture due to internal trauma and pressure on brain tissue, resulting in toxicity within the vascular system and ultimately leading to tissue infarction.[4]

EPIDEMIOLOGY:

The epidemiological study states that mostly included cross-sectional research, India's annual stroke incidence is thought to be between 105 and 152/100,000 persons.[5] The recent increase in India's life expectancy to above 60 years of age[6] has resulted in a rise in age-related non-communicable illnesses disorders, such as stroke.

RISK FACTORS:

There are several modifiable and non modifiable risk factors of stroke. The risk factors that cannot be modified include age, sex, race/ethnicity, and heredity. [7] High blood pressure, diabetes, a lack of activity drug and alcohol misuse, cholesterol, food control, and heredity are the primary modifiable risk factors for stroke.

Hypertension: Hypertension is one of the important risk factor .According to one of the studies, a blood pressure of at least 160/90 mmHg along with a history of hypertension are equally important risk factors for stroke[8,9].

High blood sugar levels: A diabetic patient have a greater chance of stoke and death by about 20%.[10,11].

Elevated cholesterol: It has a complex link with stroke, and a significant contributor to coronary heart disease.

The presence of HDL lowers the chance of having stoke. Low levels of HDL (<0.90 mmol/L) and increased levels of total triglycerides (>2.30 mmol/L)increases the risk for stroke. [12,13,14]

Alcohol and drug abuse: Alcohol and drug abuse is a very important risk factor for stroke. Even a small amount of alcohol increases the chance of hemorrhagic stroke[15,161,17]. Furthermore, there is a correlation between a higher risk of strokes of all kinds with regular use of illegal substances such as amphetamines, cannabis or marijuana, phencyclidine as PCP cocaine, heroin, or the chemical called as LSD.[18]

Smoking: The chance of having a stroke is increased by twice for average smokers compared to persons who are not smoking. 15% of deaths are caused by smoking in stroke. According to research, quitting smoking lowers one's relative chance of suffering a stroke, but long-term exposure to smoking in public raises the chances of stroke by thirty percent [19,20,21].

ETIOLOGY:

A hemorrhagic stroke can result from an artery rupturing or leaking, while an ischemic stroke might be caused by arterial blockage or narrowing.[22] Numerous drug classes have been linked to ischemic and hemorrhagic stroke. Some of the drug class such as using oral contraceptives, NSAIDs drugs, and various psychoactive substances can induce ischemic stroke.[23] While estrogen replacement therapy may lower the risk of stroke, contraceptive pills appear to modestly raise it.[24]

SIGNS&SYMPTOMS:

The traditional symptoms of stoke include hemiparesis, facial weakness, aphasia, dysarthria, diplopia, hemi-body weakness, and other vision issues, and vertigo.[25-26]

DIAGNOSIS:

Basically, imaging methods are employed to diagnose stroke patients. They are CT perfusion, MRI, MRA angiography, MR perfusion, non-contrast CT, and CT. [27] For the purpose of

diagnosing and choosing patients for endovascular therapy, CT perfusion and Computed Tomography angiography are frequently employed [28].

MANAGEMENT:

Thrombolytic Therapy: The medications used to treat IV thrombosis are designed to stimulate the production of fibrinolysin, which catalyses the clot blocking the cerebral arteries breaking apart. [29] For the treatment of stroke symptoms, another class of thrombolytics is utilized, which comprises of both fibrin andnon-fibrin medications. While in the non-fibrin activators, the medications included such as streptokinase and staphylokinase, which converts plasminogen to plasmin indirectly, fibrin activators, such as alteplase, reteplase, and tenecteplase, do so directly.[30]

Anticoagulants*:* Heparins are administered either intravenously or subcutaneously to provide a favourable recovery of stroke. Sulphated polysaccharide unfractionalised heparin inhibits factor Xa and deactivates thrombin by attaching to antithrombin. Heparinoids are glycosaminoglycans that catalyse the inhibition of thrombin by heparin co-factor 2. In the end, all heparins inhibit fibrin formation and subsequent thrombosis.[31]

Statin therapy: The primary purpose of statins is to lower the risk element for stroke. In the statin medications we mostly used or preferred medication is atorvastatin.[32] Statins have the potential to stabilize atherosclerosis, reduce blood cholesterol levels, enhance endothelial function, and suppress inflammation[33,34]. By lowering serum cholesterol levels, statins help prevent medications to treat stroke patients.[35,36]

Intra-arterial thrombolysis (IAT):An alternative treatment for acute stroke is intra-arterial thrombolysis (IAT). Expert physicians and angiographic procedures are necessary for this type of treatment, it works best in the first six hours after MCA blockage [37].

Blockers of the sodium (Na+) channel: These medicines have been used to protect neurons. They stop neurons from dying and lessen damage to white matter. Mexiletine of dose 150 to 200 mg 2 to 3 times a day has shown promise in treating ischemic stroke.[38]

Glucose management**:** Glucose management by lowering the blood glucose level is an important determinant factor for stroke. The majority of stroke patients had hyperglycaemia levels higher than 6.0 mmol/L i.e., (108 mg/dl),which exacerbated the condition by causing lipid peroxidation and tissue cell breakdown in the affected area[39]

Antiplatelet therapy**:** This treatment reduces the chances of stroke and is used to treat acute ischemic stroke. Controlling transient ischemic attacks (TIAs) and non-cardioembolic strokes is also crucial. Among the medications given to stroke victims in the early stages of their attack, combining aspirin and clopidogrel, prasugrel, or ticagrelor for dual antiplatelet therapy has gained popularity; numerous studies have examined the safety and effectiveness of this combination treatment. It has been suggested that starting aspirin and clopidogrel combined therapy within 24 hours of a stroke and continuing it for 4–12 weeks will maximize its benefits[40].

Neural restoration: An alternative treatment to neuronal protection is neural healing. It is not time-bound because its purpose is to regenerate tissue after harm has already occurred, however it works best when given 24 hours after a stroke attack[41].

Rehabilitation: People who have a stroke may experience both transient and chronic impairments. Following a stroke, speech, occupational skills, mobility, and cognitive abilities may all be the focus of therapy throughoutrehabilitation.[42]

MATERIALS:

RESEARCH DESIGN: The study on assessment of drug utilisation pattern for stroke patients

in tertiary care hospital is assessed through a Retrospective study, in a Parul Sevashram Hospital, Waghodia, Vadodara.

RESEARCH SITE: Parul Sevashram Hospital, Parul University, Vadodara, Gujarat, India

NO. OF SAMPLE COLLECTED:154 PATIENTS.

SOURCE OF DATA: Data was collected from Medical Record Department in Parul sevashram hospital, which includes male and female both.

DATA ANALYSIS: Data were collected from medical record department and then statistically analysed. Various graphs, figures are used to interpret the data which is analyzed.

RESULTS

1. AGE WISE DISTRIBUTION: From the below figure (figure 1) it can be concluded that the study whichis carried out among 154 patients gives a brief overview of the incidence of stroke among the patients whose age ranges from 31 to 81 or above. The study states that the incidence of strokeis maximum between the age group of 46-60 which consists of 68 patients and which is followed by the next age group of 61-80 which consists of 57 patients.

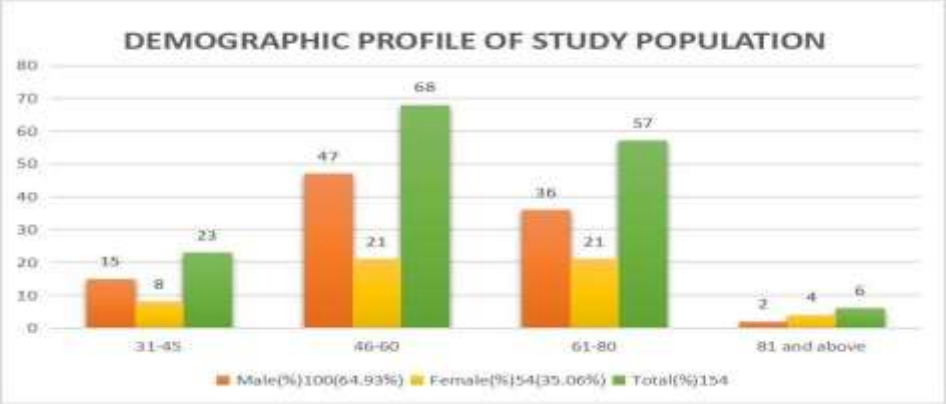


FIGURE 1: DEMOGRAPHIC PROFILE OF STUDY POPULATION

2.REGION WISE DISTRIBUTION: In this demographic data distribution region wise data shows that the maximum number of patients came from urban region includes a percentage of 62(95) and 38(59) percentage of people came from rural region (Figure 2)

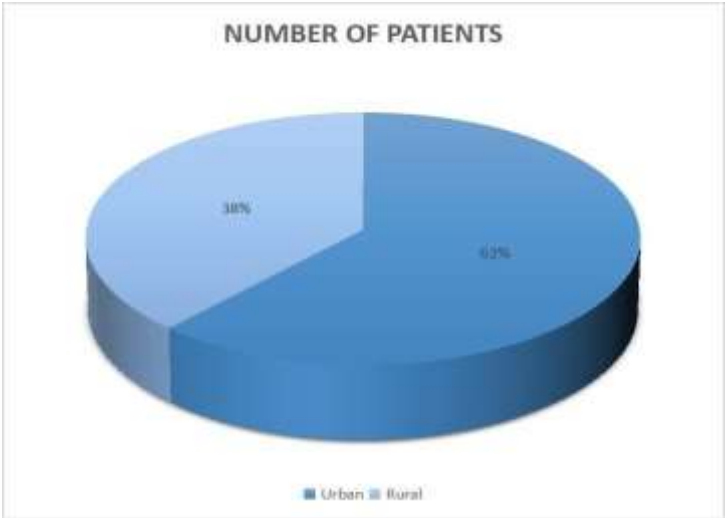
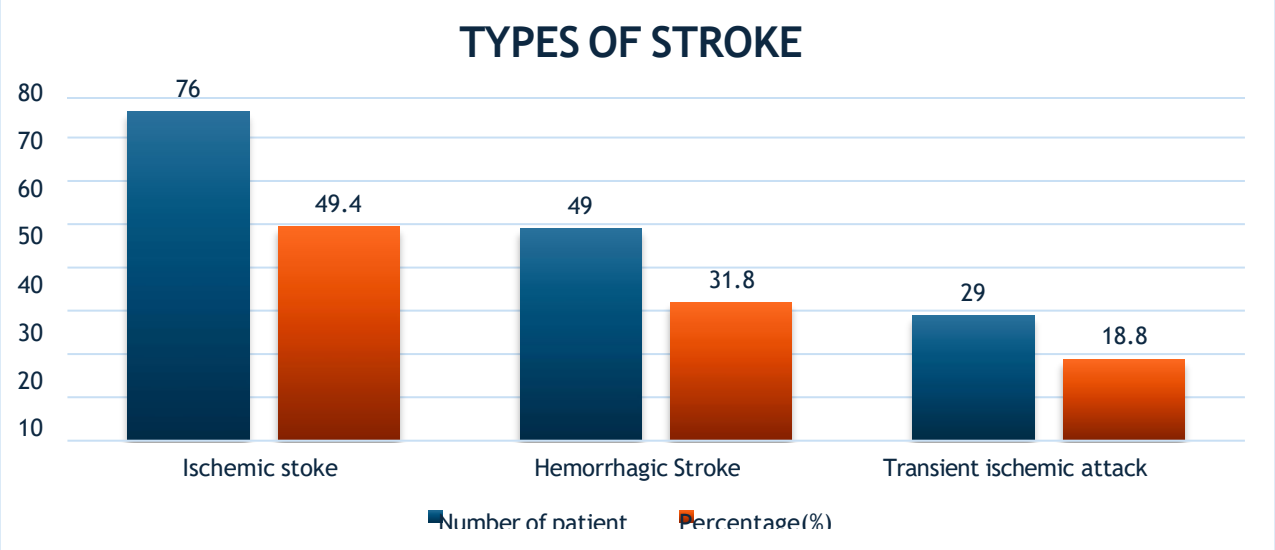


FIGURE 2: REGION WISE DISTRIBUTION

3. TYPE OF STROKE PATIENTS: The study overview that of the total population 48.4% patients are considered to be suffering from ischemic stroke, 31.8% from hemorrhagic stroke and 18.8% from transient ischemic attack. (Figure 3).

FIGURE 3: TYPES OF STROKE



4. VARIOUS TYPES OF ADDICTION IN STROKE PATIENTS: In this study data, we have seen that maximum number of people was having stroke with no addiction with the percentage of 42.2 but many people were tobacco chewer with the percentageof 40.3 and there were also other addiction like smoker addicted people having a percentage of 29.2 and alcoholic patient percentage is 21.4. (Table 4 & Figure 4).

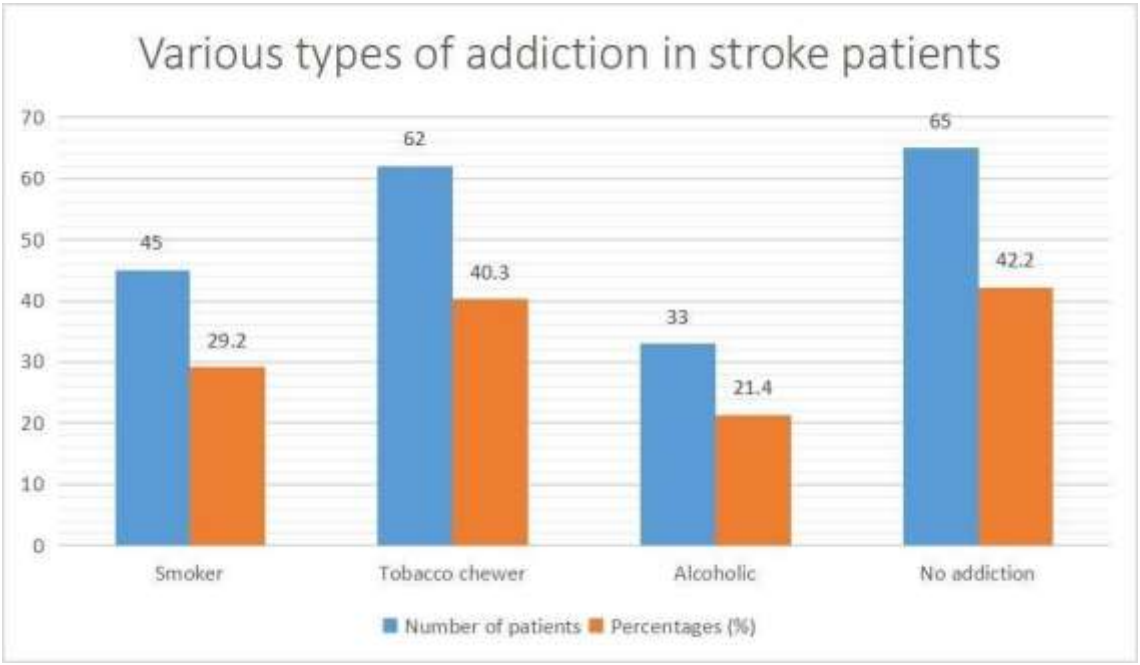


FIGURE 4: VARIOUS TYPE OF ADDICTION IN STROKE

5. VARIOUS RISK FACTOR AND CO MORBIDITIES ASSOCIATED WITH STROKE: Out of the total study population, 76.1% patients were having risk factor of hypertension, 42.2%patients were having risk factor of high cholesterol level 36.7%patients were having riskfactor of diabetes and 9.2% patients were having risk factor of obesity.as per

the result its conformed that maximum people having hypertension as a greater risk factor of associating stroke as follow high cholesterol level is the 2nd highest risk factor of associating stoke.

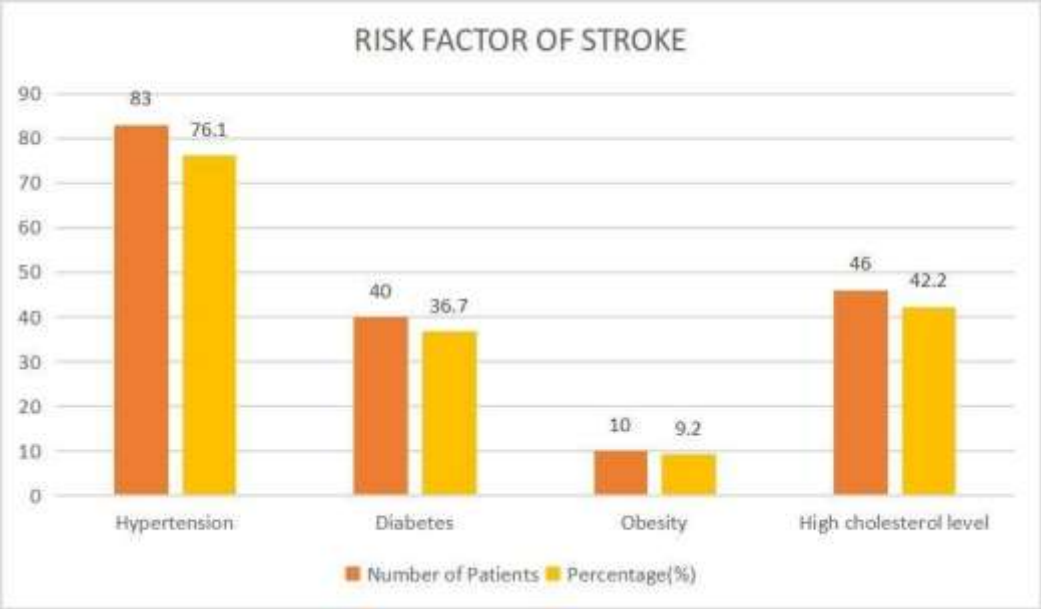


FIGURE 5: VARIOUS RISK FACTORS ASSOCIATED WITH STROKE

6. GROUP OF DRUGS PRESCRIBED IN STROKE PATIENTS: In this graphical data of drug therapy in stroke patient we have seen that the most common therapy which is used in particular collected population data that is the combination of three class of drug like statins, anti-platelets and anti-coagulant with the percentage of 93.2,93.8,34.9with according to this there are many drugs is used for the co morbidities which is associated with stroke like for hypertension they used hypertensive drug with the percentage of 62.3 and with that if patient is having seizure and psychic illness they were using anti-epileptic drugs andcerebral activator with the percentage of 24.7 in other therapy if patient was having oedema forthe stroke then they were using osmotic diuretics drugs with the percentage of 30.8 and othersdrug were sedative ,antibiotic, laxative etc.

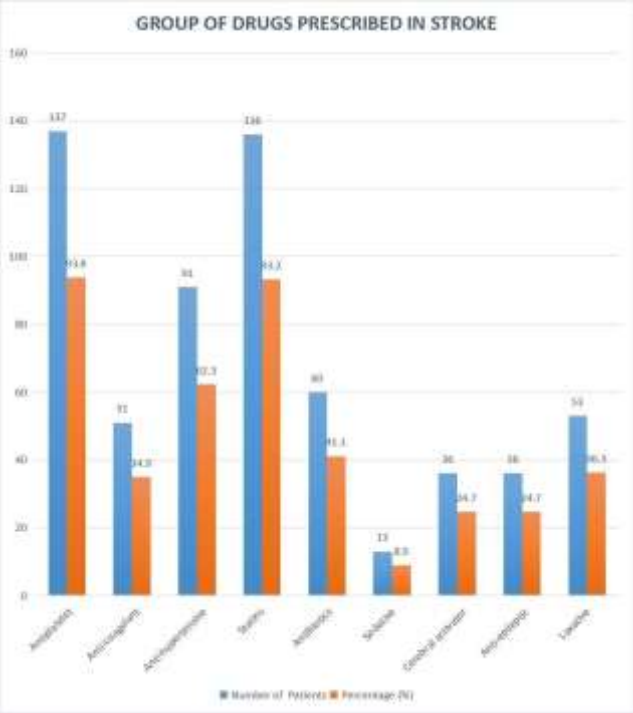


FIGURE 6: GROUP OF DRUGS PRESCRIBED IN STROKE PATIENTS

7. INDIVIDUAL AGENTS IN EACH CATEGORY OF DRUGS PRESCRIBED IN OUR SET UP:

TYPE OF DRUG	NO.OF PATIENTS	PERCENTAGE %
Anticoagulants:	**93**	**60.38**
Enoxaparin	42	45.16
Dalteparin	16	17.20
Heparin	35	37.63
Antiplatelet drugs:	**154**	**100**
Aspirin	149	96.75
Clopidogrel	135	87.66
Aspirin + Clopidogrel	3	1.94
Antihypertensive:	**103**	**66.88**
Beta blocker (Metoprolol, Propranolol, Atenolol)	29	28.15
Mixed Alpha + Beta blockers (carvedilol, labetalol)	7	6.80
Calcium channel blockers (Nifedipine, Amlodipine)	53	51.45
Angiotensin converting enzyme inhibitor (Ramipril, Enalapril)	9	8.73

Angiotensin receptor antagonist (Telmisartan)	5	4.85
Lipid lowering agents:	**129**	**83.76**
Atorvastatin	78	60.46
Rosuvastatin	51	39.53
Cerebral activators:	**14**	**9.09**
Citicholine	6	42.85
Piracetam	8	57.14
Antibiotics:	**70**	**45.45**
Amoxicillin + Clavulanic acid	2	2.85
Ceftriaxone	42	60
Cefixime	20	28.57
Metronidazole	6	8.57
Antiepileptic:	**15**	**9.74**
Phenytoin	10	66.66
Valproate	5	33.33
Diuretics:	**68**	**44.15**
Mannitol	28	41.17
Furosemide	40	58.82
Laxatives:	48	31.16
Lactulose	39	81.25
Cremaffin	9	18.75

Anticoagulant Therapy: From the above study of the individual patient receiving anticoagulant therapy overall 60.38%of individual is under the Anticoagulant Therapy . The data which is collected from a particular group of population estimates that three types of Anticoagulant drugs are been used by the population namely Enoxaparin, Dalteparin & Heparin with the percentage of 45% ,17% & 38% respectively (Table 7 & Figure 7).

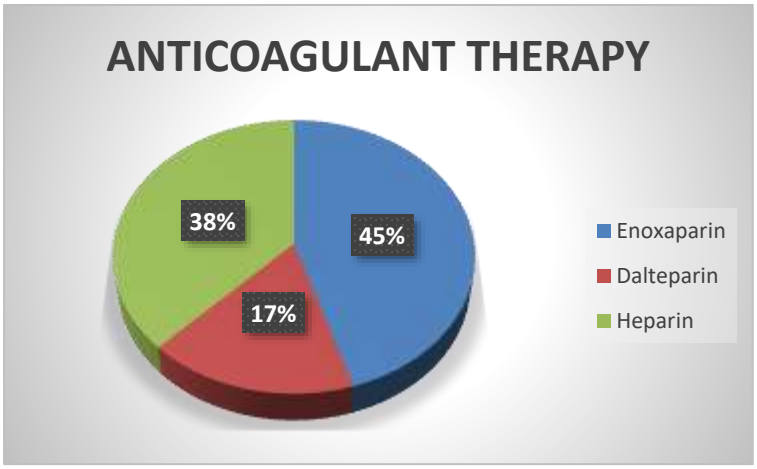


FIGURE 7: DISTRIBUTION OF PATIENT RECEIVING ANTICOAGULANTTHERAPY

Antiplatelet Therapy: The above diagrammatic representation describes the kind of Antiplatelet drugs used by the individual patient in the population. The study interprets that 96.75% of patient is receiving Aspirin 87.66% of patient is receiving Clopidogrel and 1.94% of patient is receiving Aspirin+Clopidogrel drugs. Thus, the study estimates that there is 100% overall usage of Antiplatelet drugs by the population. (Table 7 & Figure 8).

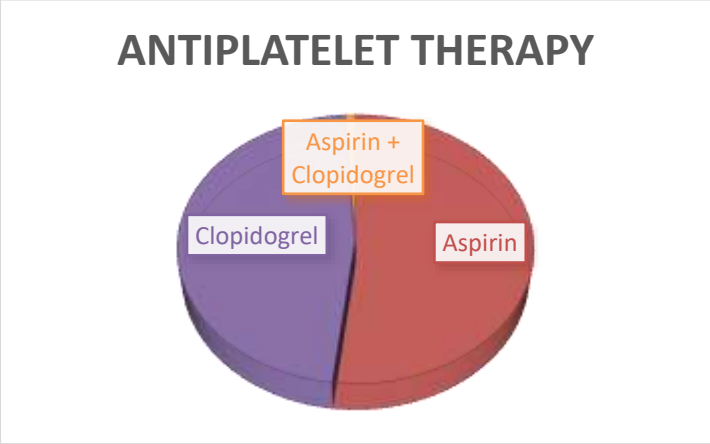


FIGURE 8: DISTRIBUTION OF PATIENT RECEIVING ANTIPLATELET THERAPY

Antihypertensive Therapy: The above diagrammatic representation estimates the overall usage of 66.88% of Antihypertensive drugs which includes 28% of Beta blocker (Metoprolol, Propranolol, Atenolol) , 7% of Mixed Alpha + Beta blockers (carvedilol, labetalol), 51% of Calcium channelblockers (Nifedipine, Amlodipine) ,9% of Angiotensin converting enzyme inhibitor (Ramipril, Enalapril),5% of Angiotensin receptor antagonist (Telmisartan) respectively. (Table 7& Figure9).

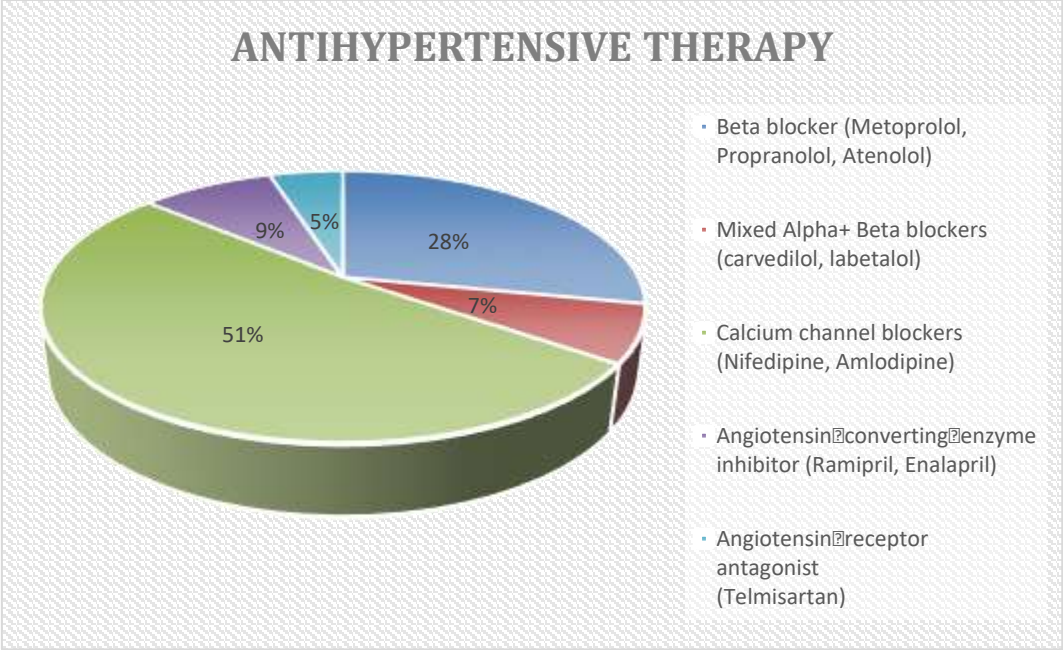


FIGURE 9: DISTRIBUTION OF PATIENT RECEIVING ANTI-HYPERTENSIVE THERAP

Lipid Lowering Agents: The study interprets the usage of lipid lowering agents at a percentage of 83.76 %. The lipid lowering drugs which are used by the population are Atorvastatin& Rosuvastatin at a percentage of 60.46%& 39.53 % respectively. (Table 7& Figure 10).

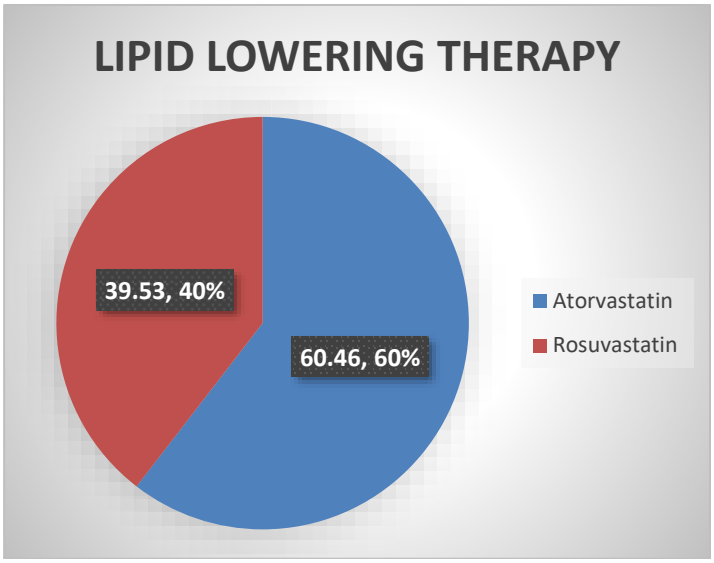


FIGURE 10: DISTRIBUTION OF PATIENT RECEIVING LIPID LOWERINGTHERAPY

Cerebral Activators Therapy: The diagrammatic representation interprets that 9% patients are overall using the cerebral Activators drugs including 43% of Citicholine and 57.14% Piracetam respectively. (Table 7& Figure 11).

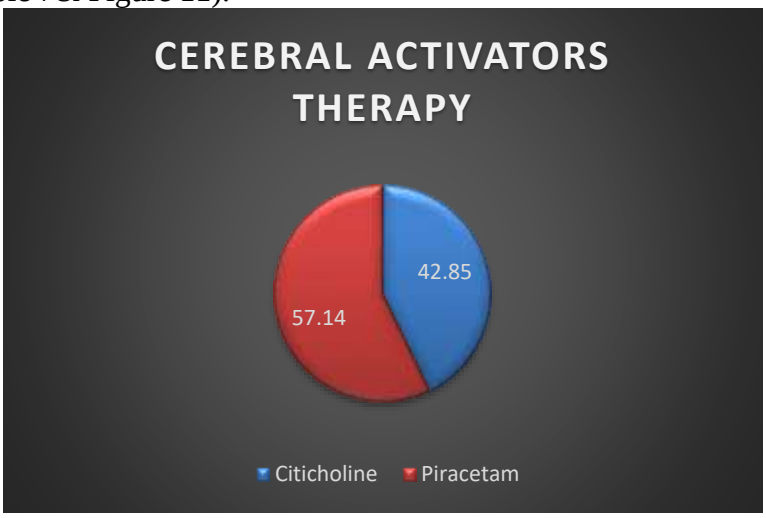


FIGURE 11: DISTRIBUTION OF PATIENT RECEIVING CEREBRALACTIVATORS THERAPY

Antibiotics Therapy: As per the study the data which is collected estimates that there is overall usage of 45.45 % ofantibiotics used by the patient of overall population which includes 2.85% usage of Amoxicillin + Clavulanic acid ,60% usage of Ceftriaxone,28.57 % usage of Cefixime, 8.57% usage ofMetronidazole respectively. (Table 7 & Figure 12).

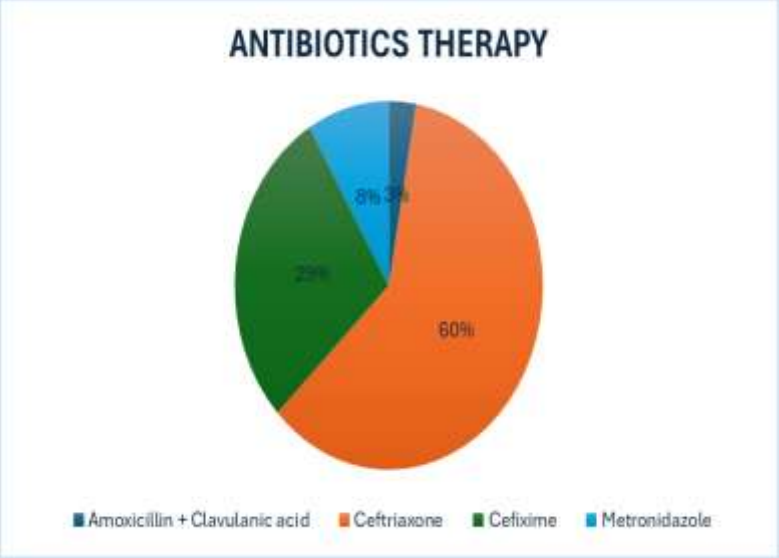


FIGURE 12: DISTRIBUTION OF PATIENT RECEIVING ANTIBIOTICS THERAPY

Antiepileptic Therapy: As per the study the data which is collected represents that there is an overall usage of 9.74 % of antiepileptic drugs which includes 66.66% & 33.33% of usage of Phenytoin & Valproate respectively. (Table 7& Figure 13).

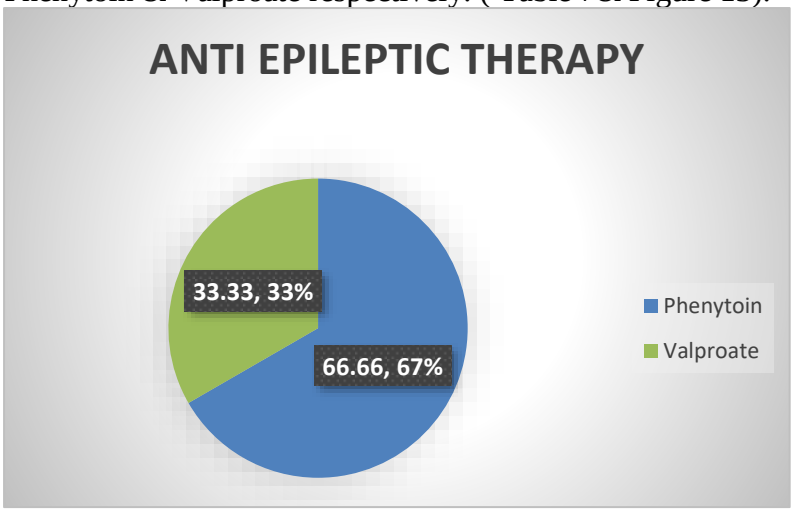


FIGURE 13: DISTRIBUTION OF PATIENT RECEIVING ANTI EPILEPTIC THERAPY

Diuretics Therapy: As per the study the data which is gathered interprets that there is an overall usage of 44.15% of Diuretics drugs .These group of drugs which are used by the patient of the particular population includes usage of 41.17% of Mannitol & usage of 58.82% of Furosemide respectively. (Table 7& Figure 14.)

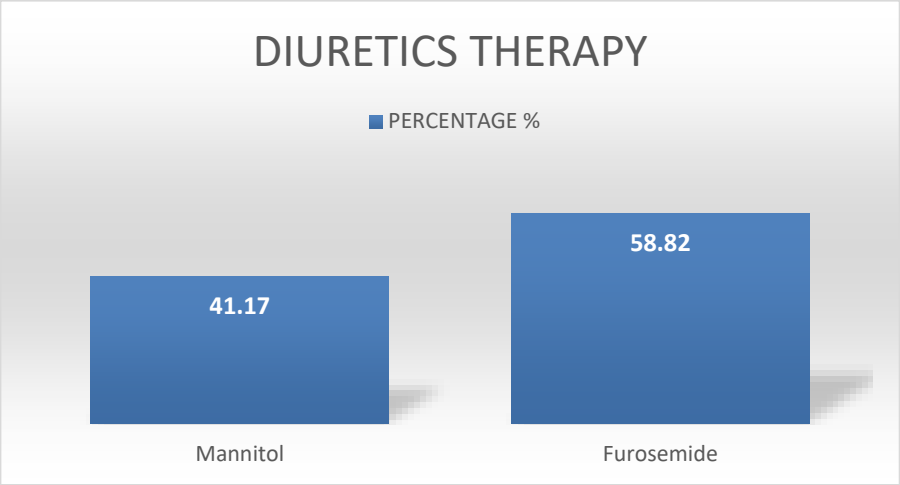


FIGURE 14: DISTRIBUTION OF PATIENT RECEIVING DIURETICSTHERAPY

Laxatives Therapy: As per the study and the diagrammatic representation the data which is gathered represents theoverall usage of 31.16% of laxatives by the population which includes two types of drugs namely Lactulose & Cremaffin. The usage of Lactulose among the population is 81.25 % & theusage of Cremaffin among the population is 18.75% respectively. (Table 7&Figure 15).

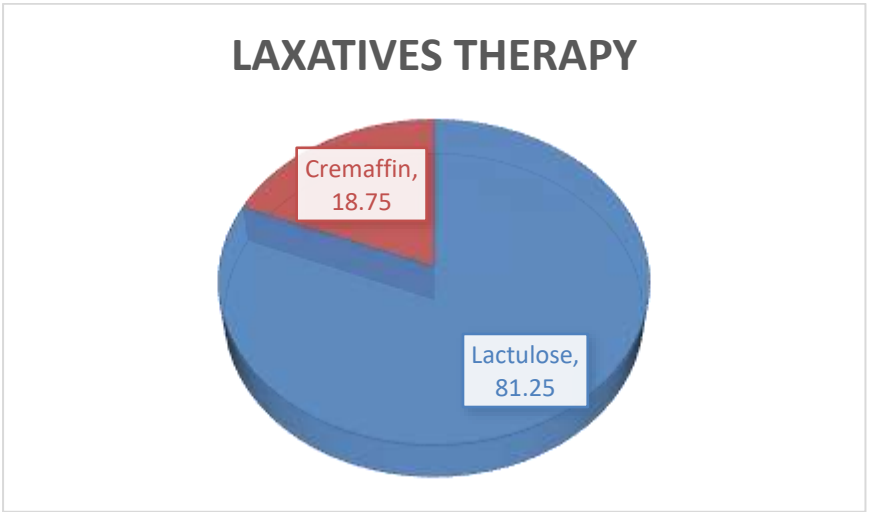


FIGURE 15: DISTRIBUTION OF PATIENT RECEIVING LAXATIVESTHERAPY

DISCUSSION

The whole study is based on the drug usage in the stroke patients who are admitted in a tertiary care hospital. This analysis revealed several notable trends and areas for consideration in clinical practice and research. The retrospective study of six months duration was carried out in a tertiary care hospital to evaluate the prescribing pattern of drugs used in patients diagnosed with stroke.

In our study population of 154 patients 100(64.93%) were male and 54(35.06%) were female, and based on the age distribution the population taken was above 30 years old.
Within 31-45 age there were total of 23 patients in which 15 were male and 8 were females. In the age group between 46-60 age, the total patients were 68 out of 154 in which 47 were males and 21 were females. Similarly, within the age group of 61-80, the total patients diagnosed with

stroke were 57 in which 36 were males and 21 were females. Lastly, above the age of 80 only 6 patients were there.

In the total of 154 patients, when distributed region wise in urban and rural area then we found that 95(61.7%) patients came from urban area and 59(38.3%) patients came from rural area. Out of 154 population 76(49.4%) patients experienced ischemic stroke and 49(31.8%) patients experienced haemorrhagic stroke with 29(18.8%) patients experiencing transient ischemic attack.

In addition to drug usage in stroke patients, it's crucial to consider the impact of addiction on both the occurrence and management of strokes. Substance abuse, including alcohol, tobacco and smoking and their chronic use can lead to hypertension, cardiac problems all of which increases the risk of stroke. In our study social histories of patients of tobacco, alcohol, and smoking where tobacco 45(29.2%) and smoking (40.3%) showed higher rate of incidence as compared to alcoholic 33(21.4%) patients. No addiction was found in 65(42.2%) patients.

The most common risk factors found in the stroke patients were hypertension 83(76.1%), high cholesterol level 46(42.2%), diabetes 40(36.7%) and obesity 10(9.2%). On the basis of the result, it is confirmed that hypertension is higher in most of the population followed by high cholesterol levels as 2nd highest risk factor in the population.

Among the drug therapies the mostly used class was antiplatelets and statins therapy, followed by anti-coagulants and many other drugs used for the comorbidities. The most common therapy mostly used was the combination of three i.e., statins(93.2%), anti-platelets(93.8%) and anti-coagulants(34.9%).In anti-coagulants the most prescribes drug was Enoxaparin(45.16%) and the least use drug was Dalteparin(17.20%).In anti-platelets therapy both aspirin(96.75%) and clopidogrel(87.66%) were frequently used and combination of both were used in (1.94%).In lipid-lowering agents the mostly prescribed drug was atorvastatin(60.46%).

In co-morbidities associated with stroke patient may have hypertension so anti-hypertensives are used in the population of (62.3%) this indicate that patients with hypertension are more prone to having stroke. Patient with stroke are more prone to hospital acquired infections so for that antibiotics are prescribed for which in our study ceftriaxone (60%), cefixime (28.57%) and metronidazole (8.57%) were used also the combination of amoxicillin + clavulanic acid(2.85%) was prescribed.

In our study, diuretics were prescribed for the widening indications such as hypertension, diabetes, and heat failure which was considered rationale in stroke therapy. The most used diuretics were furosemide (58.82%), followed by mannitol (41.17%) administered to reduce intracranial edema. Other drugs classes which were used was sedatives (8.9%), cerebral activator(24.7%),anti-epileptic(24.7%), and laxatives(36.3%).

CONCLUSION

In our study ischemic stroke was more prevalent than haemorrhagic stroke. In our studymale gender was more prone to stroke attacks than that of females. The age-group of 46-60 is more common for the occurrence of stroke. The study recommends regular and periodic studies on drug utilization for improving disease management strategy and quality of life in patients. Moreover, unnecessary multifaceted prescriptions to be avoided to achieve optimal therapeutic outcomes and therapy failures in stroke patientswhich may cause increased risk of mortality and morbidity.

Hypertension and hyperlipidaemia were identified as the major risk factors in our study.Substance abuse not only increases the risk of stroke but also complicates the treatmentand rehabilitation process. Tobacco chewing is the most common addiction associatedwith the stroke patient in

this study. Antiplatelets, Statins and anti-hypertensive were found to be major drug classes utilized in the prescription pattern of stroke. The commonly used or prescribed drugs in the study was Aspirin which is the most frequently used in the class of antiplatelets followed by clopidogrel which again falls in the class of antiplatelets and from the statins, atorvastatin was the major used drug. For the co-morbidities of stroke antihypertensives were most used drug with beta blockers(metoprolol, atenolol, propranolol) in highest numbers.

REFERENCES

1. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and FuturePerspectives. Int J Mol Sci. 2020 15;21(20):7609. doi: 10.3390/ijms21207609.
2. Musuka T.D., Wilton S.B., et al., Diagnosis and management of acute ischemic stroke:Speedis critical. CMAJ. 2015;187:887–893. doi: 10.1503/cmaj.140355.
3. Broughton B.R., Reutens D.C et al., Apoptotic mechanisms after cerebral ischemia. Stroke.2009;40:e331–e339. doi: 10.1161/STROKEAHA.108.531632.
4. Flaherty M.L., Woo D., et al. Racial variations in location and risk of intracerebral hemorrhage. Stroke. 2005;36:934–937. doi: 10.1161/01.STR.0000160756.72109.95.
5. Global Burden of Disease 2017. Causes of death collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1736–1788.
6. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: Heart disease and stroke statistics--2012 update: A report from the american heart association. Circulation. 2012; 125:188–197.
7. O'Donnell M.J., Xavier D., et al. Risk factors for ischaemic and intracerebral haemorrhagicstroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3.
8. Lewington S., Clarke R., et al., Age-specific relevance of usual blood pressure to vascularmortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–1913.
9. Vermeer S.E., Sandee W., et al., Dutch TIA Trial Study Group Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. Stroke. 2006;37:1413–1417. doi: 10.1161/01.STR.0000221766.73692.0b.
10. Banerjee C., Moon Y.P., et al., Duration of diabetes and risk of ischemic stroke: The Northern Manhattan Study. Stroke. 2012; 43:1212–1217. doi: 10.1161/STROKEAHA.111.641381.
11. Iribarren C., Jacobs D.R.,et al., Low total serum cholesterol and intracerebral hemorrhagicstroke: Is the association confined to elderly men? The Kaiser Permanente Medical Care Program. Stroke. 1996;27:1993–1998. doi: 10.1161/01.STR.27.11.1993.
12. Iribarren C., Jacobs D.R.,et al., Low total serum cholesterol and intracerebral hemorrhagicstroke: Is the association confined to elderly men? The Kaiser Permanente Medical Care Program. Stroke. 1996;27:1993–1998. doi: 10.1161/01.STR.27.11.1993.
13. Denti L., Cecchetti A., et al., The role of lipid profile in determining the risk of ischemic stroke in the elderly: A case-control study. Arch. Gerontol. Geriatr. 2003;37:51–62. doi: 10.1016/S0167-4943(03)00020-7.
14. Iso H., Jacobs D.R., et al., Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N. Engl. J. Med. 1989;320:904–910. doi: 10.1056/NEJM198904063201405.

15. Gill J.S., Zezulka A.V., Shipley M.J., Gill S.K., Beevers D.G. Stroke and alcohol consumption. N. Engl. J. Med. 1986;315:1041–1046. doi: 10.1056/NEJM198610233151701.
16. Hillbom M., Numminen H., Juvela S. Recent heavy drinking of alcohol and embolic stroke.Stroke. 1999;30:2307–2312. doi: 10.1161/01.STR.30.11.2307
17. Klatsky A.L., Armstrong M.A., et al., Alcohol drinking and risk of hospitalization for ischemic stroke. Am. J. Cardiol. 2001;88:703–706. doi: 10.1016/S0002-9149(01)01824-0.
18. Esse K., Fossati-Bellani M., et al., Epidemic of illicit drug use, mechanisms of action/addiction and stroke as a health hazard. Brain Behav. 2011;1:44–54. doi: 10.1002/brb3.7.
19. Bhat V.M., Cole J.W, et al., Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. Stroke. 2008;39:2439–2443. doi: 10.1161/STROKEAHA.107.510073.
20. Song Y.M., Cho H.J. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: A cohort study in korean men. Stroke. 2008;39:2432–2438. doi: 10.1161/STROKEAHA.107.512632.
21. Shinton R., Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ. 1989;298:789–794. doi: 10.1136/bmj.298.6676.789
22. Etiology of stroke, Panel, JP Mohr, Gregory W Albers, Pierre Amarenco, Viken L Babikian,José Biller, Robin L Brey, Bruce Coull, J Donald Easton, Camilo R Gomez, Cathy M Helgason,Carlos S Kase, Patrick M Pullicino, Alexander GG Turpie
23. Ostroumova T.M., Ostroumova O.D., Filippova Y.A. Drug-induced ischemic stroke. Medical Council. 2021;(12):42–49.
24. The role of drugs in the etiology of stroke, Michael A Kelly, Philip B Gorelick, Dan Mirza,Clinical neuropharmacology 15 (4), 249-275, 1992.
25. Lisabeth LD, Brown DL, Hughes R, Majersik JJ, Morgenstern LB. Acute stroke symptoms: comparing women and men. Stroke. 2009 Jun;40(6):20316.doi:10.1161/STROKEAHA.109.546812. Epub 2009 FeB PMID: 19228858.
26. Labiche LA, Chan W, et al., Sex and acute stroke presentation. Ann Emerg Med. 2002; *40*:453–460.
27. Hasan TF, Rabinstein AA, et al.. Diagnosis and management of acute ischemic stroke. *Mayo Clin Proc.* (2018) 93:523–38. 10.1016/j.mayocp.2018.02.013
28. Campbell BCV, Donnan GA, et al.. Endovascular stent thrombectomy: the new standard ofcare for large vessel ischaemic stroke. *Lancet Neurol.* (2015) 14:846–54. 10.1016/S1474-4422(15)00140-4
29. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group Tissue plasminogen activator for acute ischemic stroke. *N. Engl. J. Med.* 1995;333:1581– 1587. doi: 10.1056/NEJM199512143332401.
30. Barreto A.D. Intravenous thrombolytics for ischemic stroke. *Neurotherapeutics.* 2011;8:388–399. doi: 10.1007/s13311-011-0049-x.
31. Wang X, Ouyang M et al., Anticoagulants for acute ischaemic stroke. Cochrane Database System Rev. 2021 Oct 22;10(10):CD000024. doi:10.1002/14651858.CD000024.pub5. PMID:34676532; PMCID: PMC8530823.
32. Tramacere I, Boncoraglio GB, et al. Comparison of statins for secondary prevention in

patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. BMC Med. 2019 Mar;17((1)):67.
33. Toso A, Leoncini M, De Servi S. Statins and myocardial infarction: from secondary "prevention" to early "treatment". J Cardiovasc Med (Hagerstown). 2019;20:220–2.
34. Bahrami A, Bo S, Jamialahmadi T, et al.. Effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on ageing: molecular mechanisms. Ageing Res Rev. 2020;58:101024.

35. Liu CH, Lin YS, Sung PS, et al.. Colchicine use and risks of stroke recurrence in acute non- cardiogenic ischemic stroke patients: a population-based cohort study. J Pers Med. 2021;11:935.
36. Moustafa B, Testai FD. Efficacy and safety of PCSK9 inhibitors in stroke prevention. J Stroke Cerebrovasc Dis. 2021;30:106057.
37. Segura T., Calleja S., Jordan J. Recommendations and treatment strategies for the management of acute ischemic stroke. Expert Opin. Pharmacother. 2008;9:1071–1085. doi: 10.1517/14656566.9.7.1071.
38. Hewitt K.E., Stys P.K., Lesiuk H.J. The use-dependent sodium channel blocker mexiletineis neuroprotective against global ischemic injury. Brain Res. 2001; 898:281–287. doi: 10.1016/S0006-8993(01)02195-3.
39. Lindsberg P.J., Roine R.O. Hyperglycaemia in acute stroke. *Stroke.* 2004; 35:363–364. doi:10.1161/01.STR.0000115297.92132.84.
40. Stringberg A., Camden R., et al., Update on Dual Antiplatelet Therapy for Secondary StrokePrevention. Mo. Med. 2019;116:303–307.
41. Chopp M., Li Y., Zhang Z.G. Mechanisms underlying improved recovery of neurological function after stroke in the rodent after treatment with neurorestorative cellbased therapies. *Stroke.* 2009;40:S143–S145. doi: 10.1161/STROKEAHA.108.533141.
42. Dobkin B.H. Strategies for stroke rehabilitation. Lancet Neurol. 2004;3:528–536. doi: 10.1016/S1474-4422(04).