Original Article

Comparative effectiveness of dual antiplatelet therapy versus monotherapy in patients with ischemic stroke

Rahmah A. Algarni, PharmD, Abdulhamid A. Althagafi, PharmD, Samah Alshehri, Pharm D, Mohannad Alshibani, PharmD, Omar Alshargi, MPharm.

ABSTRACT

الأهداف: مقارنة فعالية المعالجة الأحادية لمنع تجمع صفائح الدم بالاسبرين أو الكلوبيدوجريل والمعالجة المزدوجة في السكتة الدماغية.

المنهجية: هذه الدراسة عبارة عن تصميم اترابي استرجاعي أحادية المركز. أجريت مراجعة سجلات مرضى السكتة الدماغية الافقارية المؤرشفة من يناير 2015م إلى أكتوبر 2019م في مستشفى جامعة الملك عبد العزيز. كانت نقاط النهاية الأولية هي تكرار السكتة الدماغية، وتكرار دخول المريض المستشفى ، والوفيات الناجمة عن جميع الأسباب. كانت النتائج الثانوية هي أحداث النزف واثر تكرار دخول المريض المستشفى الناتج عن احتشاء عضلة القلب والسكتة والذبحة الصدرية.

النتائج: كان متوسط الوقت لتكرار السكتة الدماغية 15 شهرًا (95%فترة الثقة، 9.872 إلى 23.01) للمعالجة المزدوجة بمانعات تجمعات الصفائح مقارنة بـ 20.4 شهرًا (95% فترة الثقة، 9.872 إلى 30.928). بالنسبة لمتوسط فترات البقاء على قيد الحياة حتى الوفيات الناجمة عن جميع الأسباب فقد كانت الفترة 14.1 شهرًا (95% فترة الثقة، 8.173 إلى 19.97) للعلاج الأحادي مقارنة بـ 8 أشهر (95% فترة الثقة، 2.893 إلى 13.107). لم يكن هناك انخفاض ذو دلالة إحصائية في الخطر اللحظي من تكرار حدوث النزف (HR = 1.27،95% فترة الثقة = 0.59 إلى 2.72، p=0.54) ، إعادة دخول المريض المستشفى (HR=0.95، فترة الثقة 95%، 0.59 إلى 1.48، p=0.77) ، ومعدل الوفاة (HR=1.04، فترة الثقة 95%، 0.48 إلى 2.26، p=0.92) بين مجموعتي العلاج الأحادي والمزدوج في أي وقت.

الخلاصة: العلاج المزدوج المضاد للصفائح الدم لم يكن افضل من العلاج الأحادي في الحد من تكرار النزف وأحداث الوفيات في المرضى الخاضعين للدراسة. كلا طريقتي المعالجة يملكان أحداث نزيف متشابهة (كبيرة وصغيرة). ومع ذلك، فإن معدلات إعادة الدخول إلى المستشفى نتيجة السكتة الدماغية والذبحة الصدرية واحتشاء عضلة القلب كانت أكثر في العلاج المزدوج مقارنة بالعلاج الأحادي.

Objectives: To compare the effectiveness of aspirin-clopidogrel dual antiplatelet therapy (DAPT) with aspirin or clopidogrel antiplatelet monotherapy (AM) in patients with ischemic stroke.

Methods: It was a single-center, retrospective cross-sectional study of medical records of ischemic stroke patients admitted at King Abdulaziz University Hospital between January 2015 and October 2019. The primary endpoints were ischemic stroke recurrence, rehospitalization, and all-cause mortality between DAPT and AM. Kaplan-Meier and Cox proportional hazard analyses were employed in univariate and multivariate time-to-event analyses.

Results: The median time to recurrence of ischemic stroke was 15.0 months (95% confidence interval [CI], 8.586–23.01) for DAPT and 20.4 months (95% CI, 9.872–30.928) for the AM. The median survival time until all-cause mortality was 8.0 months (95% CI, 2.893–13.107) for DAPT and 14.1 months (95% CI, 8.173–19.97) for the AM. No statistically significant reductions in the instantaneous risks of recurrence (hazard ratio [HR], 1.27; 95% CI, 0.59–2.72; p=0.54), re-hospitalization (HR, 0.95; 95% CI, 0.59–1.48; p= 0.77), and mortality (HR, 1.04; 95% CI, 0.48–2.26; p=0.92) were found between the DAPT and AM groups.

Conclusion: The DAPT was not superior to AM in reducing recurrence and mortality events in patients with ischemic stroke. Rehospitalization due to the sequelae of the composite of stroke, angina, and myocardial infarction was higher in the DAPT group.

Neurosciences 2023; Vol. 28 (4): 220-226
doi: 10.17712/nsj.2023.4.20230021

From the Department of Pharmacy (Algarni), King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia, from the Department of Pharmacy Practice (Althagafi, Alshehri, Alshibani), Faculty of Pharmacy, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia, and from the College of Pharmacy (Alshargi), Riyadh Elm University, Riyadh, Kingdom of Saudi Arabia.

Received 20th February 2023. Accepted 3rd July 2023.

Address correspondence and reprint request to: Dr. Rahmah A. Algarni, Department of Pharmacy, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Email: Raalgarni@kau.edu.sa
ORCID ID: https://orcid.org/0000-0002-9590-0647

Stroke is one of the leading causes of death and disability globally. It is associated with significant economic consequences.[1] According to a study, most stroke incidents in the Kingdom of Saudi Arabia (KSA) each year are ischemic strokes (79–87%). It occurs in the range of 43–57 per 100,000 people. Compared to other Middle Eastern nations, the fatality rate from stroke is significant (27%) in KSA.[2] Reduced mortality and morbidity are attainable only with effective treatment of ischemic stroke.[3] Ischemic stroke results from the abrupt loss of blood flow to a portion of the brain. The loss of blood flow to the brain could be due to thrombotic or embolic obstruction of a cerebral artery. Ischemic stroke is more frequent than hemorrhagic stroke.[4] There is an urgent need for improvements in secondary prevention to lower the risks of recurrence or mortality within five years after a first stroke.[5,6] Cohort studies have revealed a decrease in the risk of recurrent stroke and transient ischemic (TIA) attacks with advancement in secondary stroke prevention measures.[7]

Antiplatelet therapy is a crucial preventive intervention against stroke recurrence, ensuing vascular problems, and death.[8–10] The most widely utilized medications include aspirin, clopidogrel, and combinations of antiplatelet therapy like aspirin and clopidogrel. Following a stroke, single antiplatelet medicines have a well-established role, and their use has been supported by several substantial research. Dual antiplatelet therapy (DAPT) use after an ischemic stroke is more debatable and has recently been proven useful in certain situations. Although early studies of chronic DAPT in stroke showed no additional benefit and increased bleeding over single antiplatelets, DAPT with aspirin and clopidogrel was found to help treat coronary artery disease.[11,12] However, recent research indicates that DAPT may reduce stroke risk more than a single antiplatelet therapy because it more effectively inhibits platelet activation pathways. In contrast, clinical trials comparing DAPT to single antiplatelet therapy for secondary prevention have not consistently demonstrated a decrease in recurrent stroke and frequently showed increases in the frequency of bleeding.[13]

A lower risk of stroke recurrence was seen with the combination of clopidogrel and aspirin (clopidogrel-aspirin) compared to aspirin alone in the Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial and the Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke (POINT) trial. However, selecting the best dual antiplatelet medication regimen for stroke patients necessitates an individualized approach based on the patient's characteristics. In comparison to aspirin alone, clopidogrel with aspirin reduced the incidence of stroke recurrence in non-carriers of the cytochrome P450 2C19 (CYP2C19) loss-of-function (LOF) alleles, but not in carriers. As a result, clopidogrel may not offer the carriers any significant benefit over aspirin alone in terms of preventing strokes. Recently, the POINT sub-research was unable to replicate the findings from the CHANCE trial, probably due to a lack of statistical power.[14]

The use of DAPT can continue for 21 to 90 days following a mild stroke or TIA, according to the 2019 Guidelines for the Management of Acute Ischemic Stroke. After 90 days, it is unclear whether antiplatelet administration should continue as monotherapy or dual treatment. Additionally, there are still questions about the best antiplatelet approach to deploy and if DAPT can be safely used on a larger patient group.[15] This research compared the efficacy of DAPT, which uses aspirin and clopidogrel in combination, with antiplatelet monotherapy (AM), which uses either aspirin or clopidogrel, in patients with ischemic stroke in a tertiary care hospital in Saudi Arabia.

Methods.

Study design. This study employed a retrospective cross-sectional design. Data were retrieved from the medical record of ischemic stroke patients admitted between 2015 and 2019.

Setting. The study was conducted at King Abdulaziz University (KAU) Hospital in the city of Jeddah, in the western region of KSA. The patients' data collected include the age, gender, and physicians' diagnosis of ischemic stroke. Data collected on antiplatelet therapy received include monotherapy with aspirin or clopidogrel or DAPT with aspirin and clopidogrel. Other data collected include risk factors such as hypertension, diabetes mellitus, dyslipidemia, heart failure, ischemic heart disease, cancer, and chronic kidney disease. The patients' data were reviewed for up to 59 months (4.9 years).

Participants. The participants of this study include all eligible patients diagnosed with ischemic stroke hospitalized in the Neurology Department of KAU Hospital between 2015 and 2019. The inclusion criteria included: (1) patients aged >18 years admitted with at least a first attack of ischemic stroke; (2) patients who had ischemic stroke and received AM or DAPT. The exclusion criteria were: (1) patients admitted with hemorrhagic stroke or TIA; (2) pediatric patients aged <18 years; (3) patients who died during the first hospitalization. The study participants were divided into 2 groups, DAPT or AM group for comparison.

Variables. The time to recurrence of ischemic stroke was used as a prognostic measure to compare the superiority of DAPT over AM and vice versa. Other primary endpoints were re-hospitalization and all-cause mortality at the end of the 59-month follow-up period. The secondary outcomes were evaluated as the occurrence of the composites of myocardial infarction, stroke, and angina, as well as minor and major bleeding events.

Data sources/measurement. Data was obtained from the patient's medical records. The time to the occurrence of the primary endpoints was used to measure the variables of interest. The time to recurrence of ischemic stroke was estimated as the number of months between the initial and a subsequent stroke episode despite being on either DAPT or AM. The time to re-hospitalization was estimated as the number of months between the initial and subsequent hospitalization for a second stroke episode. The time to all-cause mortality was estimated as the number of months between the initial hospitalization for an ischemic stroke and the death from all causes. The occurrence of the composites of myocardial infarction, stroke, and angina, as well as minor and major bleeding episodes, were analyzed as the secondary outcomes.

Ethical approval. Ethical approval was obtained from the Institutional Review Board of the KAU (reference number: 729-19) before the commencement of the data collection. The confidentiality and anonymity of the patients were maintained during and after the study periods.

Statistical analysis. For statistical analysis, IBMCorp's Statistical Package for the Social Sciences 20.0 (Armonk, New York, USA) software was used. Continuous variables were presented as mean±standard deviation (SD), and independent t-test was used to determine the statistical significance of between-group differences. The Pearson Chi-square test was used to evaluate between-group differences for categorical variables, which were provided as frequency (%).

Kaplan-Meier (KM) and Cox proportional hazard (PH) analyses were employed in univariate and multivariate time-to-event analyses. Prior to the KM analysis, the data were scrutinized for compliance to mutual and collective exhaustivity with regard to event status, independence of censoring and occurrence of the target event, and other KM statistical assumptions.[16] Results were presented as KM survival curves indicating the cumulative survival rate according to the time-to-target event for each antiplatelet intervention. To investigate the equality between the KM survival curves, the null hypothesis that there was no inequality in the survival distribution was tested using the log-rank test (LRT). The null hypothesis was accepted if the test

Table 1 - Demographic and clinical characteristics of the patients.

Variables	AM Group (n=173)	DAPT Group (n=178)	*P*-value
Age (years)	62 (±13.0)	63 (±14.0)	0.457
Gender, n (%)			
Male	119 (52)	110 (48)	0.170
Risk factor, n (%)			
Hypertension	127 (52)	119 (48)	0.180
Diabetes mellitus	107 (50)	106 (50)	0.660
Chronic kidney disease	8 (40)	12 (60)	0.390
Ischemic heart disease	33 (70)	14 (30)	<0.001
Dyslipidemia	19 (49)	20 (51)	0.940
Cancer	1 (17)	5 (83)	0.110
Hepatic diseases	1 (50)	1 (50)	0.980
Heart failure	7 (54)	6 (46)	0.740
Smoking status	18 (44)	23 (56)	0.460
Dosing			
Aspirin	81mg	-	-
Clopidogrel	75mg	-	-
Aspirin + Clopidogrel	-	81mg + 75mg	-

AM - Antiplatelets therapy with Aspirin or Clopidogrel, DAPT - Dual Antiplatelet therapy with Aspirin + Clopidogrel

Table 2 - Cox proportional hazard analysis for comparison of the recurrence of ischemic stroke between the dual antiplatelet therapy and monotherapy groups after adjusting for baseline covariates.

Covariate	Stroke recurrence		Hazard ratio (95% confidence interval)	*P*-value
	DAPT	AM		
Hypertension	14	10	12.23 (0.95–15.12)	0.060
Diabetes mellitus	12	7	0.41 (0.07–2.36)	0.320
Dyslipidemia	1	3	2.33 (0.41–13.33)	0.340
Ischemic heart disease	3	5	0.42 (0.06–3.00)	0.380
Heavy smocking	4	1	0.18 (0.01–3.07)	0.230

DAPT - Dual Antiplatelet Therapy with Aspirin + Clopidogrel, AM - Antiplatelet Monotherapy with Aspirin or Clopidogrel

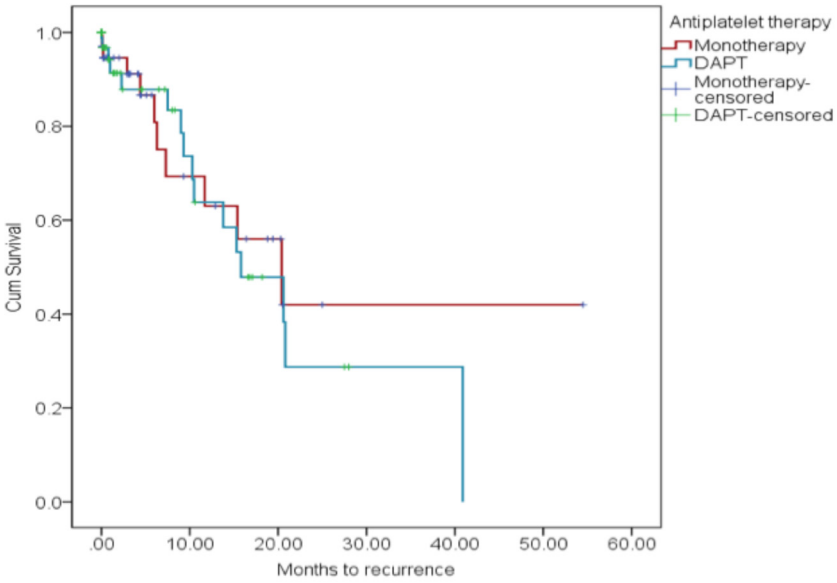

Figure 1 - Cumulative survival probability according to time (months) to recurrence of ischemic stroke for the groups of patients who received aspirin-clopidogrel dual antiplatelet therapy (DAPT) and monotherapy (aspirin or clopidogrel).

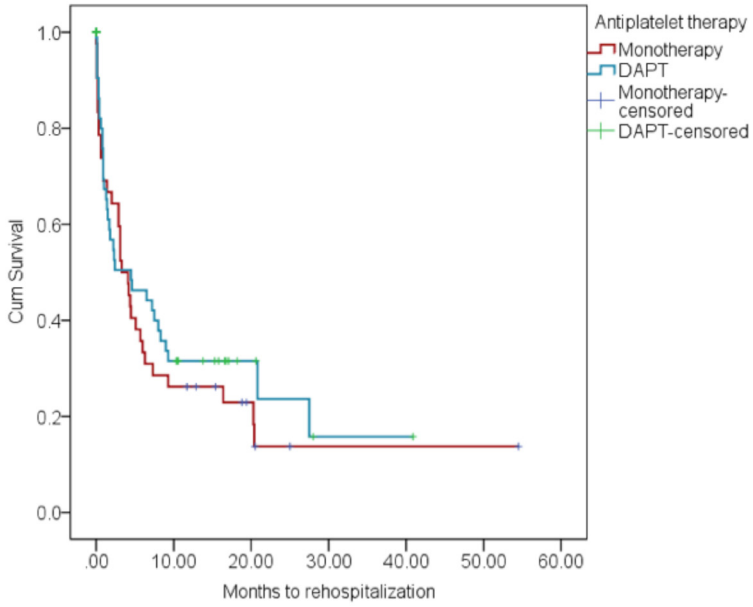

Figure 2 - Kaplan-Meier survival function for comparison of month to rehospitalization between the groups of patients who received aspirin-clopidogrel dual antiplatelet therapy (DAPT) and monotherapy (aspirin or clopidogrel) for the management of ischemic stroke.

statistical value (χ_Logrank^2) was smaller than the critical value. Cox proportional hazard (PH) regression analysis was employed to model the hazard function as adjusted for the impact of the baseline imbalances of the clinical covariates.[17] Statistical significance was considered at *p*-values <0.05 throughout.

Results. Table 1 showed the demographic and clinical characteristics of the patients. A total of 1159 patients' records folders were screened. However, 351 patients (229 males and 122 females; mean age: 62.5±13.5 years) met the inclusion criteria and were considered in the final analysis. The majority of the

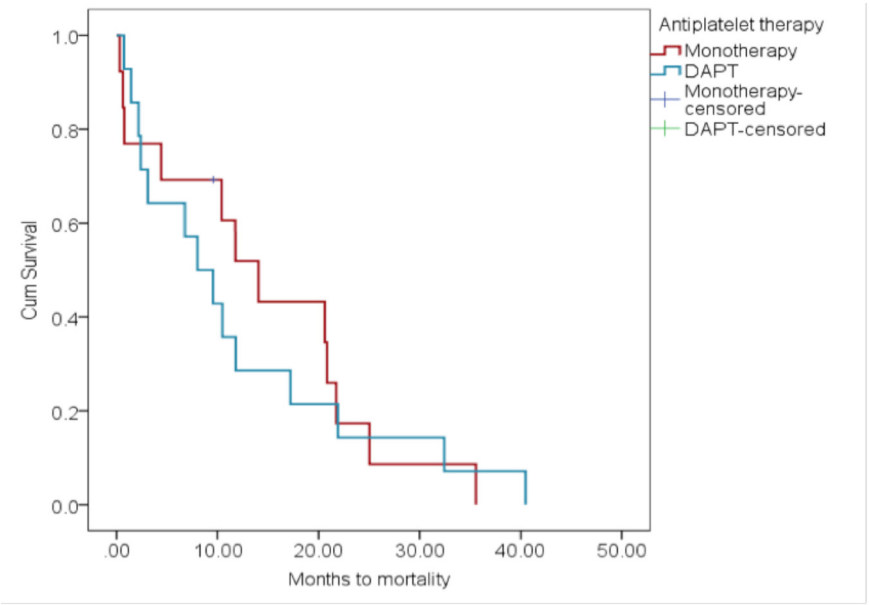

Figure 3 - Cumulative survival probability according to time (months) to all-cause mortality for the groups of patients who received aspirin-clopidogrel dual antiplatelet therapy (DAPT) and monotherapy (aspirin or clopidogrel) for the management of ischemic stroke.

patients, 178 (50.7%) received DAPT. There were no significant differences in the ages and genders of the patients between the DAPT and AM groups at $p<0.05$.

The median times to recurrence of ischemic stroke were 15 months (95% CI, 8.586–23.01) and 20.4 months (95% CI, 9.872–30.928) for DAPT and AM respectively. However, the survival functions indicated an overlapping survival distribution (**Figure 1**). The test of equality of the distributions using the LRT indicated sufficient evidence to accept that, there was no significant difference [χ^2(1)=0.308, p=0.579] in the time to recurrence of ischemic stroke between the 2 groups.

Similarly, there was no significant difference in the median survival times for re-hospitalization between the groups {DAPT, 4.5 months (95% CI, 0.00–9.769) and AM, 4.1 months (95% CI, 2.752–5.448), LRT [χ^2(1)=0.308, p=0.579], **Figure 2**}.

Figure 3 showed the median survival times from the date of admission for ischemic stroke until all-cause mortality; 8.00 months (95% CI, 2.893–13.107) and 14.071 months (95% CI, 8.173–19.97) for DAPT and AM respectively. The LRT indicated no statistically significant differences, [χ2(1)=0.069, p=0.793] in the survival distribution, and therefore suggests that DAPT lacks superior efficacy over AM.

Table 2 showed the Cox proportional hazard analysis comparing the recurrence of ischemic stroke between the DAPT and monotherapy groups after adjusting for baseline risk factor. There were no significant differences in the time-to-stroke recurrence between the DAPT and AM even after adjusting for the baseline risk factors.

Re-hospitalization due to sequelae of the composites of myocardial infarction, stroke, and angina was higher in the DAPT than in the AM group, (15.2% vs 8.1%, p=0.040). However, major and minor bleeding events did not differ significantly between the DAPT and AM groups, (3.4% vs 1.7%, p=0.500).

Discussion. This single-center retrospective cross-sectional study principally utilized a time-to-event analysis to compare the prognosis of ischemic stroke between patients who received oral DAPT and AM. Antiplatelet therapy is the principal component of pharmacotherapy for the management of recurrent stroke. The mean age of the patients and the higher proportion of males reported in this study were similar to those reported in earlier studies.[18]

Our findings showed a shorter median time to recurrence with a longer median time to re-hospitalization in the DAPT group. Conversely, there was a longer median time to all-cause mortality in the AM group. However, all these differences were not statistically significant to accept the superiority of the DAPT over the AM.

Numerous studies have compared the relative effectiveness of DAPT and AM treatments in

lowering the incidence of major cardiovascular events in individuals with ischemic stroke. Our results in the present study support several other findings that aspirin-clopidogrel DAPT does not significantly reduce the risk of major vascular events compared to monotherapy.[12,19] However, research has shown that DAPT is more effective than AM for reducing recurrent ischemic stroke and hence has a role in early secondary stroke prevention when started shortly after a high-risk TIA or minor stroke and sustained for 21 to 90 days.[13] The DAPT was not linked to a decreased risk of ischemic stroke when started within 1 to 2 months of a stroke or TIA and continued for 2 to 3 years, although it was linked to more bleeding episodes and is hence not advised in this situation. Contrarily, our research found no significant difference in the frequency of bleeding episodes between the DAPT and AM groups throughout the 4.9 months leading up to event observation. In general, the declining survival step functions of antiplatelet drugs suggest a good prognostic advantage in terms of lowering the frequency of recurrence, rehospitalization, and mortality rate. When the various antiplatelet drugs were evaluated with baseline clinical data from the study participants, no divergence of preferred qualities was also seen. Our results are in line with earlier studies in that DAPT with clopidogrel and aspirin has not convincingly shown prevention of recurrent events in long-term prevention compared to aspirin or clopidogrel AM, even though our results did not show a significant increase in the incidence of bleeding events between the groups over the 4.9-month observation.[13,18,19] Therefore, if absolute benefit is predicted, specific use should be carefully considered on a case-by-case basis.

Study limitations. First, this study is a small single-center study, hence generalizability of its findings cannot be possible. However, the study might have provided local data for future research and local clinical decision.

Second, because it is observational research, there was a higher risk of bias, including confounding, information, and selection bias. These concerns were addressed through the use of univariate and multivariate time-to-events analyses. However, this might not entirely remove them.

Interpretation. The patients in the aspirin-clopidogrel DAPT and aspirin or clopidogrel monotherapy groups demonstrated similar prognostic propensity in terms of reduced stroke recurrence.

Conclusions. Aspirin-clopidogrel DAPT was not superior to aspirin or clopidogrel monotherapy in reducing recurrence and mortality events in the patients in this study. The therapies were associated with similar bleeding events. However, the rate of re-hospitalization due to the sequelae of the composite of stroke, angina, and myocardial infarction was higher in the aspirin-clopidogrel dual antiplatelet therapy group compared to the monotherapy group.

References

1. Tadi Prasanna FL. Acute Stroke. [Updated 2023 Feb 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan [Internet]. 2023 [cited 2023 May 26]. p. 88-100.
2. Muhammad AT, Aljohani MM. Stroke In KSA ; Epidemiology And Clinical Delineation. ***Majmaah J Heal Sci*** 2021; 9: 109-120.
3. Franziska H, Fred R. Management of Acute Ischemic Stroke. ***Concise Defin Rev*** 2020; 48: 1654-1663.
4. Edward CJ. Ischemic stroke [Internet]. Medical Crossfire. 2022 [cited 2023 May 26]. Available from: https://emedicine.medscape.com/article/1916852-overview
5. Yiping C, Neil W, Yu G, Iain T, Christiana K, Ling Y, et al. Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0·5 million Chinese adults. ***Lancet Glob Heal*** 2020; 8: e580-e590.
6. Stahmeyer JT, Stubenrauch S, Geyer S, Weissenborn K, Eberhard S. The Frequency and Timing of Recurrent Stroke. ***Dtsch Arztebl Int*** 2019; 116: 711-717.
7. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack; A guideline from the American Heart Association/American Stroke Association. ***Stroke*** 20211; 52: e364–e467.
8. Jourdi G, Godier A, Lordkipanidzé M, Marquis-Gravel G, Gaussem P. Antiplatelet Therapy for Atherothrombotic Disease in 2022—From Population to Patient-Centered Approaches. ***Front Cardiovasc Med*** 2022; 9: 1-19.
9. Del Giovane C, Boncoraglio GB, Bertù L, Banzi R, Tramacere I. Antiplatelet drugs for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. ***BMC Neurol*** 2021; 21: 1-10.
10. Minhas JS, Chithiramohan T, Wang X, Barnes SC, Clough RH, Kadicheeni M, et al. Oral antiplatelet therapy for acute ischaemic stroke (Review). ***Cochrane Database Syst Rev*** 2022; 1: 1–16.
11. Pace WD, Earl A, Bryant C. Antiplatelet Therapy for Secondary Prevention of Ischemic Stroke. ***Cardiovascular*** 2020; 45: HS8-HS12.
12. Dong J, Wang F, Sundararajan S. Use of Dual Antiplatelet Therapy following Ischemic Stroke. ***Stroke*** 2020; 51: e78-e80.
13. Brown DL, Levine DA, Albright K, Kapral MK, Leung LY, Reeves MJ, et al. Benefits and Risks of Dual Versus Single Antiplatelet Therapy for Secondary Stroke Prevention. ***Stroke*** 2021; 52: e468-e479.
14. Wang Y, Johnston C, Bath PM, Meng X, Jing J, Xie X, et al. Clopidogrel with aspirin in High-risk patients with Acute Non-disabling Cerebrovascular Events II (CHANCE-2): Rationale and design of a multicentre randomised trial. ***Stroke Vasc Neurol*** 2021; 6: 280-285.

15. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. ***Stroke*** 2019; 50: e344–e418.
16. Pessoa RLC, Antunes-foschini R, Rocha EM. Survival analysis (Kaplan-Meier curves): a method to predict the future. ***Arq Bras Oftalmol*** 2020; 83: 33-35.
17. Deo SV. Survival analysis — part 2 : Cox proportional hazards model. ***Indian J Thorac Cardiovasc Surg*** 2021; 37: 229–233.
18. Lee HL, Kim JT, Lee JS, Park MS, Choi KH, Cho KH, et al. Comparative Effectiveness of Dual Antiplatelet Therapy With Aspirin and Clopidogrel Versus Aspirin Monotherapy in Mild-to-Moderate Acute Ischemic Stroke According to the Risk of Recurrent Stroke: An Analysis of 15 000 Patients From a Nationwide, Multicent. ***Circ Cardiovasc Qual Outcomes*** 2020; 13: e006474.
19. Hackam DG, Spence JD. Antiplatelet therapy in ischemic stroke and transient ischemic attack: An overview of major trials and meta-analyses. ***Stroke*** 2019; 50: 773-778.