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ORIGINAL ARTICLE

Antiplatelet Therapy for Secondary Prevention in Patients with Ischaemic Stroke and Transient Ischaemic Attack: A Retrospective Cohort Study in Malaysia

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ABSTRAK

Dalam kajian ini, kami menilai hasil klinikal terapi antiplatelet untuk pencegahan sekunder berikutan diagnosis strok iskemia atau serangan iskemia sementara (TIA). Ini adalah kajian kohort retrospektif yang merangkumi pesakit dewasa dengan strok iskemia atau TIA yang baru didiagnosis antara tahun 2014 dan 2017 dengan menggunakan data daripada pangkalan data di Malaysia. Pesakit dikategorikan kepada pengguna terapi antiplatelet tunggal (SAPT) dan terapi dwi antiplatelet (DAPT). Hasil utama adalah gabungan strok, infarksi miokardium dan kematian semua sebab dalam tempoh 90 hari dan 1 tahun. Hasil keselamatan adalah pendarahan. Di antara 3344 pesakit strok, 8.1% menerima DAPT dan 91.2% menerima SAPT. Insiden terkumpul satu tahun bagi peristiwa komposit ialah 16.0 dan 7.2 masing-masing bagi setiap 100 orang-tahun untuk SAPT dan DAPT.

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Analisis padanan skor kecenderungan model bahaya Cox menunjukkan DAPT mengurangkan risiko kejadian komposit (nisbah bahaya (HR) 0.48; 95% CI 0.25-0.91) dan strok berulang (HR 0.38; 95% CI 0.16-0.92). Keputusan adalah tidak signifikan untuk hasil individu lain dan hasil 90 hari. Risiko pendarahan tidak jauh berbeza antara SAPT dan DAPT. Rawatan dengan DAPT selepas strok iskemia/TIA dikaitkan dengan pengurangan risiko kejadian komposit (strok, infarksi miokardium atau kematian) dan strok berulang dalam tempoh 1 tahun.

Kata kunci: Antiplatelet; pencegahan sekunder; strok

ABSTRACT

In this study, we evaluated clinical outcomes of antiplatelet therapy for secondary prevention in ischaemic stroke and transient ischaemic attack (TIA) patients. This was a retrospective cohort study that included patients with newly diagnosed ischaemic stroke or TIA between 2014 and 2017 using data from routine practice in Malaysia. Patients were grouped into single antiplatelet therapy (SAPT) and dual antiplatelet therapy (DAPT) users. Primary outcome was composite of stroke, myocardial infarction, and all-cause death in 90 days and 1 year. Safety outcome was major bleeding events. Among 3344 stroke patients, 8.1% received DAPT and 91.2% received SAPT. The 1-year cumulative incidence of composite events was 16.0 and 7.2 per 100 person-years for SAPT and DAPT, respectively. Propensity score-matched analysis of Cox hazard model showed DAPT reduced the risk of composite event (hazard ratio (HR) 0.48; 95% CI 0.25-0.91) and recurrent stroke (HR 0.38; 95% CI 0.16-0.92) in 1-year follow-up. Results were not significant for myocardial infarction, all-cause death, and 90-day outcomes. The risks of bleeding were not significantly different between SAPT and DAPT. Treatment with DAPT after an ischaemic stroke/TIA was associated with reduced risk of the composite events (stroke, myocardial infarction, or death) and recurrent stroke at 1 year.

Keywords: Antiplatelet; secondary prevention; stroke

INTRODUCTION

Approximately 6-18% of stroke patients experienced a recurrence within one year (Kolmos et al. 2021). Antiplatelet therapy is the cornerstone of treatment strategies in patients who have had ischaemic stroke and has proven to be effective in preventing recurrent events. Although the role of single antiplatelet therapy (SAPT) has been established in secondary stroke prevention, dual antiplatelet therapy (DAPT) may provide more effective stroke prevention and combination of acetylsalicylic acid (ASA) plus dipyridamole is considered among first-line treatment choice (European

Stroke Organisation 2008; Kernan et al. 2014). Yet, long-term treatment with DAPT is often associated with increased risk of bleeding (Hackam & Spence 2019). However, evidence from trials followed by a systematic review suggested that patients with noncardioembolic events may benefit from DAPT when administered early and over a short-term period (Brown et al. 2021; Hao et al. 2018; Johnston et al. 2018; Wang et al. 2013).

While randomised controlled trial is the gold standard for demonstrating the efficacy of a given therapy, the results may be an overestimation of the real-world effectiveness of the intervention. Moreover, differences in disease patterns, clinical practices, and risk/benefit profiles between Asian and Western populations could result in different treatment effects and risks (Gao & Li 2010; Kim et al. 2013; Shinohara 2006). Current stroke guidelines recommend ASA for secondary prevention with other single agents as viable alternatives and combination therapy of ASA-Clopidogrel for patients with minor stroke (National Institutes of Health Stroke Scale [NIHSS] score <5) or high-risk TIA for 21 days (Powers et al. 2018; Malaysian Society of Neurosciences 2021). The objective of this study was to assess treatment patterns and clinical outcomes of antiplatelet therapy for Asian patients of multi-ethnicity who had non-cardioembolic ischaemic stroke or TIA based on data from real-world practice in Malaysia. Specifically, we aimed to describe types of antiplatelet prescribed to patients and evaluate risks of recurrent stroke, myocardial infarction, all-cause mortality, and bleeding.

MATERIALS AND METHODS

Study Design and Data Source

A retrospective cohort study of patients diagnosed with an ischaemic stroke or TIA and treated with antiplatelet therapy between January 2014 and December 2017 in Malaysia was conducted.

Two stroke registries were used to identify stroke patients: (i) the National Stroke Registry, a database for non-mandatory notifications of stroke admissions in participating hospitals in Malaysia (Aziz et al. 2015); and (ii) the Universiti Kebangsaan Malaysia Medical Centre (UKMMC) stroke registry, a hospital-based registry of stroke patients from a tertiary university hospital in Malaysia. These registries provided information on patient demographics, risk factors, stroke information, treatment, and complications. Additional information was extracted from medical charts abstraction at the respective hospitals that included inpatient and outpatient encounters and prescription details (drug type, dispensing date, duration). Outcome data was obtained from the hospitalisation database provided by the Health Informatics Centre, Ministry of Health (inpatient details, diagnoses according to the International Classification of Diseases [ICD-10]). Although this database included admission records from private hospitals, restricted information was available on patient unique identifiers

and thus limited the availability of data linkage. Therefore, only data from public hospitals were included in this study. Mortality data was retrieved from the National Registration Department. This study was approved by the review board of the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-18-379-40587). This included a waiver of informed consent due to the use of secondary data. All patient data were de-identified and anonymised before analysis.

Data Collection and Linkage

Information on stroke patients and prescriptions were retrieved from the stroke registries to form the cohort and supplemental chart review was performed by the research team at study sites which involved 10 public hospitals and one university hospital. The stroke cohort dataset was linked to the hospitalisation database and mortality database for ascertainment of outcomes. Data collection and management was carried out using Research Electronic Data Capture (REDCap) tools hosted at Clinical Research Centre, Hospital Pulau Pinang (Harris et al. 2009; Harris et al. 2019). Data linkage was performed at an individual level using a unique personal identification number. The linkage of data was performed by the research team and managed at the Institute for Clinical Research, National Institutes of Health Malaysia. De-identified data was applied for further data processing and analysis.

Study Population

Patients who met the following criteria were included in the study: (i) had a first diagnosis of ischaemic stroke or TIA between 1st January 2014 and 31st December 2017; (ii) aged 18 years and older; and (iii) prescribed with at least one antiplatelet drug upon discharge. Diagnosis of ischaemic stroke and TIA was defined as the first hospitalisation for the event with no known history of ischaemic stroke/TIA (index stroke). We excluded patients who died during hospitalisation, transferred to another facility, or died within two weeks after discharge. Patients were also excluded if they had cardioembolic stroke or if the duration of post-discharge antiplatelet prescription was less than two weeks. All patients had a minimum of 90 days and a maximum of 365 days (1-year) follow-up from the date of hospital discharge.

Drug Exposure

Exposure was defined as treatment with antiplatelet therapy (ATC code: B01AC) if at least one prescription for these drugs within 14 days of hospital discharge were found. The index prescription date was the first prescription date of antiplatelet upon discharge. Patients were followed in an "intention-to-treat" approach, where patients were followed for 365 days within the treatment group to which they were initially assigned during the index prescription. A 30-day grace period was added to the estimated prescription duration to account for irregular refills and minor non-compliance. Patients were censored in case of treatment discontinuation,

defined as the absence of a refill prescription within 30 days (plus the grace period) from the date of the last supply (Spoendlin et al. 2018). Patients were classified according to exposure to antiplatelet therapy during the index prescription into two main categories: (i) single antiplatelet therapy (SAPT); and (ii) dual antiplatelet therapy (DAPT). Treatment with DAPT usually lasted for a maximum of 21 days prior to subsequent treatment with SAPT.

Outcomes

The primary effectiveness outcome was a composite endpoint of hospitalisation for all strokes (ischaemic and haemorrhagic), myocardial infarction, or all-cause mortality within (i) 90 days and (ii) 365 days (1 year) of the index stroke. Secondary outcomes were the individual events of the composite endpoint. Safety outcome was bleeding and was defined as any report of bleeding events during the follow-up. A bleeding event included hospitalisation with a diagnosis of clinically overt bleeding that included gastrointestinal bleeding and bleeding at other sites. The list of ICD-10 codes for the outcomes was provided in Table 1. The ICD-10 codes were identified based on the review of literature on case definition (stroke, myocardial infarction, bleeding) and expert panel opinions (Blin et al. 2020; Christiansen et al. 2015). Patients were followed up from the index prescription until the occurrence of any study outcome, loss to follow-up, or day 365, whichever came first.

Covariates

Patients' baseline characteristics i.e., demographics, risk factors and comorbidities, past medication history, stroke subtypes and characteristics were included as covariates.

Statistical Analysis

Data were presented as frequency with percentages for categorical variables and means with standard deviations for continuous variables. Chi-square or Fisher exact test (categorical variables) and t-test or Mann-Whitney test (continuous variables) were used to compare the distribution of baseline characteristics between the treatment groups. Propensity score (PS) matching was performed using the MatchIt package in RStudio statistical software to generate comparable datasets between the treatment groups and to assess primary and secondary endpoints. PS were estimated using multivariable logistic regression model with the treatment status regressed on covariates measured at baseline (age, sex, ethnicity; risk factors, prior medication use, stroke characteristics, mRS at discharge, and year of diagnosis). Variables used in PS matching were measured for potential confounders (Brookhart et al. 2006). PS-matched pairs were created using nearest neighbour 1:2 matching without replacement and with a caliper width of 0.2 (Austin 2011). Balance across groups was assumed based on standardised mean difference (SMD) of <0.10.

Incidence rates were estimated

TABLE 1: List of ICD-10 codes for definition of outcomes

Outcome	ICD Code	ICD Term
Stroke, haemorrhagic	I60	Nontraumatic subarachnoid haemorrhage
	I61	Nontraumatic intracerebral haemorrhage
	I62	Other and unspecified nontraumatic intracranial haemorrhage
	I69.0	Sequelae of nontraumatic subarachnoid haemorrhage
	I69.1	Sequelae of nontraumatic intracerebral haemorrhage
	I69.2	Sequelae of other nontraumatic intracranial haemorrhage
Stroke, ischaemic	I63	Cerebral infarction
Transient ischaemic attack	G45	Transient cerebral ischemic attacks and related syndromes
Myocardial infarction	I20	Angina pectoris
	I21	Acute myocardial infarction
	I22	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
	I24	Other acute ischemic heart diseases
Bleeding	I85.0	Oesophageal varices
	K25.0	Acute gastric ulcer with haemorrhage
	K25.2	Acute gastric ulcer with both haemorrhage and perforation
	K25.4	Chronic or unspecified gastric ulcer with haemorrhage
	K25.6	Chronic or unspecified gastric ulcer with both haemorrhage and perforation
	K26.0	Acute duodenal ulcer with haemorrhage
	K26.2	Acute duodenal ulcer with both haemorrhage and perforation
	K26.4	Chronic or unspecified duodenal ulcer with haemorrhage
	K26.6	Chronic or unspecified duodenal ulcer with both haemorrhage and perforation
	K27.0	Acute peptic ulcer, site unspecified, with haemorrhage
	K27.2	Acute peptic ulcer, site unspecified, with both haemorrhage and perforation
	K27.4	Chronic or unspecified peptic ulcer, site unspecified, with haemorrhage
	K27.6	Chronic or unspecified peptic ulcer, site unspecified, with both haemorrhage and perforation
	K28.0	Acute gastrojejunal ulcer with haemorrhage
	K28.2	Acute gastrojejunal ulcer with both haemorrhage and perforation
	K28.4	Chronic or unspecified gastrojejunal ulcer with haemorrhage
	K28.6	Chronic or unspecified gastrojejunal ulcer with both haemorrhage and perforation
	K29.0	Acute gastritis
	K62.5	Haemorrhage of anus and rectum
	K92.0	Hematemesis
	K92.1	Melena
	K92.2	Gastrointestinal haemorrhage, unspecified

by calculating the number of events divided by 100 person-years of follow-up. Cox proportional hazard regression model was used to estimate hazard ratios with the corresponding 95% confidence interval to test the association between treatment groups and the outcome events. Estimates were reported in crude and adjusted (analyses in propensity-matched cohort). Analyses for secondary individual outcomes were performed accounting for the competing risk of all-cause death. Missing values for patient characteristics were coded as a separate category and reported for the

respective variables.

All statistical tests were two-tailed and p-values <0.05 were considered significant. Statistical analyses were conducted in R 4.0.2 in RStudio.

RESULTS

A total of 3344 patients hospitalised for a first-ever ischaemic stroke or TIA between 1st January 2014 and 31st December 2017 met study eligibility criteria and were included in the analysis (Figure 1). Figure 2 shows the types of antiplatelets prescribed at discharge. ASA monotherapy was most frequently prescribed (88%). Clopidogrel was prescribed to 4% of patients as monotherapy and 8% in combination with ASA. Other antiplatelet regimens were prescribed to less than 1% of patients each. Analysis of the trend in utilisation over the year showed that the overall use of DAPT increased gradually and was highest in 2017 (11.0%) compared to earlier years (2.4% in 2014; data was not shown).

Table 2 described the characteristics of the study population treated with SAPT (n=3072, 91.2%) and DAPT (n=272, 8.1%). Compared with the SAPT group, the DAPT group was younger (p=0.01) and had more males (p<0.001); had a history of ischaemic heart disease (p<0.001), and with exposure to alcohol (p<0.001) and smoking (p<0.001). The proportion of

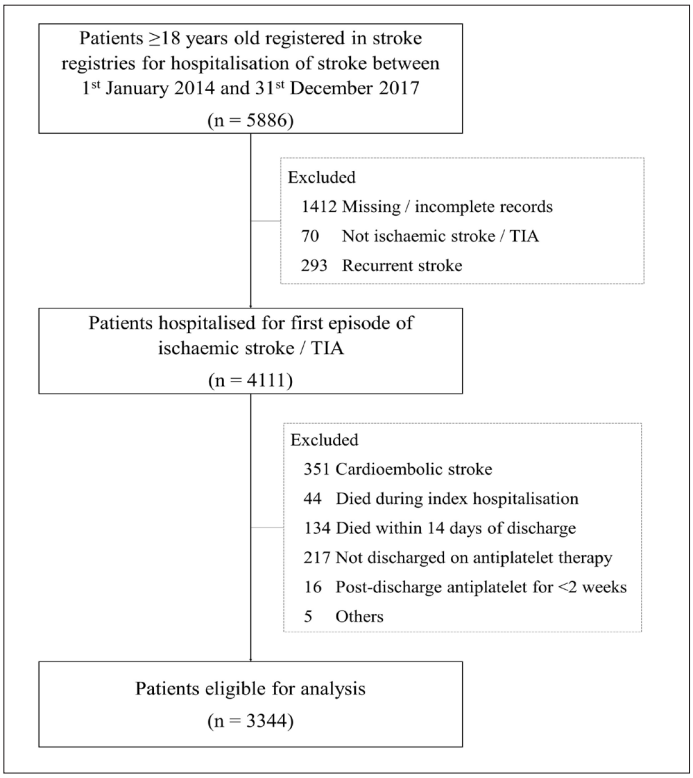

FIGURE 1: Selection flow of study population

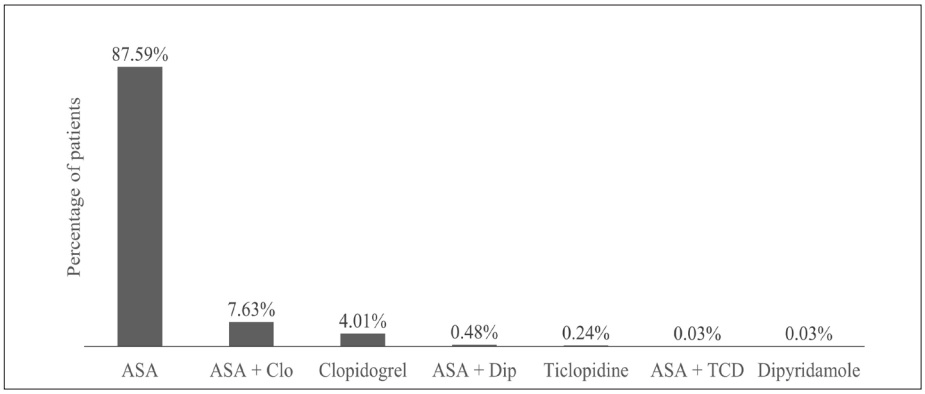

FIGURE 2: Types of antiplatelet regimen prescribed at discharge. Abbreviations: ASA=aspirin; Clo=clopidogrel; Dip=dipyridamole; TCD=ticlopidine

patients with TIA was also higher in DAPT compared to SAPT (20% versus 5%; p<0.001) and the majority had mRS of less than 3. After PS matching, 743 patients (22.2% of the original cohort) were identified for further analysis and baseline distributions were fairly balanced between SAPT and DAPT in the propensity-matched cohort (Table 2 & Figure 3).

Effectiveness Outcome

Incident rates of the outcomes at 90 days were shown in Table 3. In the unadjusted analysis, the incidence rate of the primary outcome was 10.9/100 person-years in DAPT and 35.1/100 person-years in the SAPT group, which corresponded to crude hazard ratio (HR) of 0.32 (95% CI 0.15, 0.67).

TABLE 2: Baseline characteristics of study population

	Before PSM			After PSM		
	SAPT	DAPT	P value	SAPT	DAPT	P value
Characteristic	**n = 3072**	**n = 272**		**n = 289**	**n = 289**	
Age in years, median (IQR)	61.2 (52.7, 69.7)	68.8 (51.7, 67.9)	0.02*	59.5 (51.0, 68.4)	68.9 (51.9, 67.9)	0.72#
Male, n (%)	1753 (57.1)	196 (72.1)	<0.001*	344 (71.5)	188 (71.8)	1.00
Ethnicity, n (%)			<0.001*			0.76
Malay	2361 (76.9)	121 (44.5)		241 (50.1)	120 (45.8)	
Chinese	415 (13.5)	79 (29.0)		135 (28.1)	75 (28.6)	
Indian	82 (2.7)	5 (1.8)		7 (1.5)	5 (1.9)	
Others	189 (6.2)	66 (24.3)		97 (20.2)	61 (23.3)	
Missing	25 (0.8)	1 (0.4)		1 (0.2)	1 (0.4)	
Ischaemic stroke, n (%)	2965 (96.5)	221 (81.2)	<0.001*	415 (86.3)	219 (83.6)	0.38
NIHSS Score, median (IQR)	4 (1, 8)	2 (1, 4)	<0.001*	3 (1, 6)	2 (1, 4)	0.41#
OCSP classification, n (%)			<0.001*			0.62
LACI	1483 (48.3)	157 (57.7)		281 (58.4)	155 (59.2)	
PACI	738 (24.0)	30 (11.0)		60 (12.5)	30 (11.5)	
POCI	285 (9.3)	31 (11.4)		63 (13.1)	31 (11.8)	
TACI	280 (9.1)	6 (2.2)		18 (3.7)	6 (2.3)	
Unspecified	286 (9.3)	48 (17.6)		59 (12.3)	40 (15.3)	

Risk factors, n (%)						
Hypertension	2259 (73.5)	199 (73.2)	0.95	356 (74.0)	192 (73.3)	0.90
Diabetes mellitus	1392 (45.3)	114 (41.9)	0.31	205 (42.6)	112 (42.7)	1.00
Dyslipidaemia	763 (24.8)	80 (29.4)	0.11	144 (29.9)	76 (29.0)	0.86
Ischaemic heart disease	300 (9.8)	46 (16.9)	<0.001*	88 (18.3)	43 (16.4)	0.59
Atrial fibrillation	57 (1.9)	7 (2.6)	0.55	12 (2.5)	7 (2.7)	1.00
Previous bleeding	16 (0.5)	2 (0.7)	0.98	2 (0.4)	2 (0.8)	0.93
Alcohol use	131 (4.3)	46 (16.9)	<0.001*	64 (13.3)	39 (14.9)	0.63
Current smoker	726 (23.6)	86 (31.6)	<0.001*	142 (29.5)	78 (29.8)	0.95
Medication history, n (%)						
Antiplatelet	466 (15.2)	56 (20.6)	0.023	100 (20.8)	54 (20.6)	1.00
Oral anticoagulant	21 (0.7)	2 (0.7)	1.00	3 (0.6)	2 (0.8)	1.00
Antihypertensive	1170 (38.1)	136 (50.0)	<0.001*	242 (50.3)	131 (50.0)	1.00
Antidiabetics	769 (25.0)	70 (25.7)	0.86	115 (23.9)	69 (26.3)	0.52
Lipid lowering	726 (23.6)	95 (34.9)	<0.001*	161 (33.5)	91 (34.7)	0.79
mRS at discharge, n (%)			<0.001*			0.45
0, no disability	226 (7.4)	64 (23.5)		84 (17.5)	56 (21.4)	
1, no significant disability	627 (20.4)	90 (33.1)		160 (33.3)	89 (34.0)	
2, slight disability	650 (21.2)	65 (23.9)		134 (27.9)	64 (24.4)	
3, moderate disability	659 (21.5)	22 (8.1)		28 (5.8)	22 (8.4)	
4, moderately severe disability	610 (19.9)	25 (9.2)		58 (12.1)	25 (9.5)	
5, severe disability	193 (6.3)	3 (1.1)		7 (1.5)	3 (1.1)	
Missing	107 (3.5)	3 (1.1)		10 (2.1)	3 (1.1)	
Year of stroke diagnosis, n (%)			<0.001			0.99
2014	652 (21.2)	16 (5.9)		28 (5.8)	16 (6.1)	
2015	711 (23.1)	55 (20.2)		99 (20.6)	52 (19.8)	
2016	830 (27.0)	92 (33.8)		160 (33.3)	89 (34.0)	
2017	879 (28.6)	109 (40.1)		194 (40.3)	105 (40.1)	

Abbreviations: DAPT=dual antiplatelet therapy; IQR=interquartile range; LACI=lacunar infarct; mRS= modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; OCSP=Oxfordshire Community Stroke Project; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; PSM=propensity score matching; SAPT=single antiplatelet therapy; TACI=total anterior circulation infarct.
P-values were computed from Chi-square test or Fisher's exact test (n<10).
#Age and NIHSS score were not normally distributed and P-values were computed from Mann-Whitney test
*indicates significant difference, p value less than 0.05 (p<0.05)

All-cause mortality was numerically lower in the DAPT group than in the SAPT group (rate difference -17.2/100 person-years) while no difference was observed for stroke. No myocardial infarction event was recorded in the DAPT group during the 90-day follow-up. In the analysis of the PS-matched cohort, the incidence rate of both primary and secondary outcomes continued to be lower in the DAPT group, but the hazard ratios were not statistically significant for the composite endpoint (HR 0.48; 95% CI 0.21,1.11), stroke (HR 0.60; 95% CI 0.24, 1.50), and all-cause death (HR 0.22; 95% CI 0.03, 1.79) (Table 3).

Table 4 showed 1-year cumulative event rates for the respective outcomes. A significant reduction in the risk of composite endpoint was observed for DAPT compared to SAPT within 1 year of follow-up with the crude HR of 0.32 (95% CI 0.18, 0.58). Consistent result was observed in PS-matched analysis with HR of 0.48 (95% CI 0.25, 0.91). For secondary outcomes, a significant reduction in the risk of stroke was

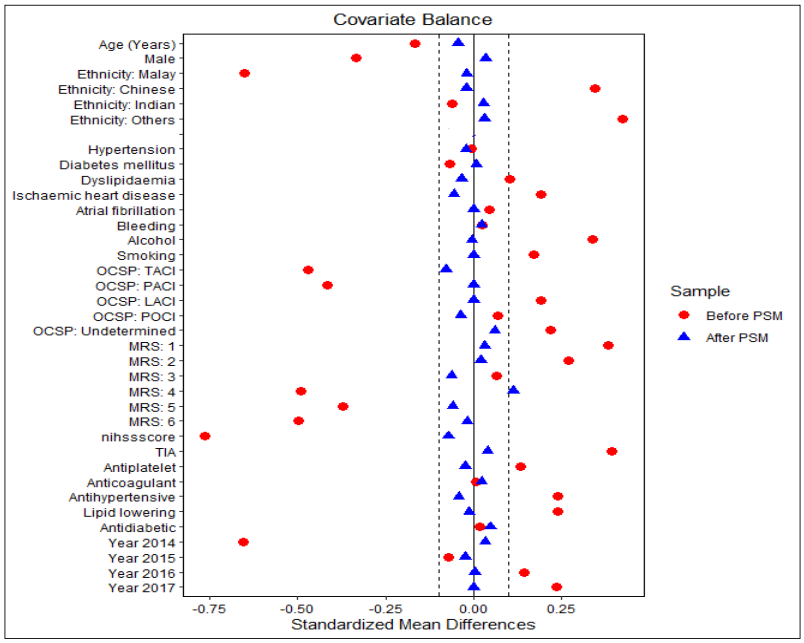

FIGURE 3: Standardised mean difference of covariates for estimating propensity score before and after propensity score matching

TABLE 3: Effectiveness outcome event rates for 90-day follow-up and hazard ratios of DAPT compared to SAPT

	Before PSM			After PSM		
	SAPT	**DAPT**	**Crude HR (95& CI)**	**SAPT**	**DAPT**	**Crude HR (95& CI)**
N	**3072**	**272**		**481**	**262**	
Primary outcome						
Composite endpoint of stroke, MI, or death						
No. of events (%)	240 (7.8%)	7 (2.6%)		26 (5.4%)	7 (2.7%)	
Incidence rate‡	35.12	10.96	0.32 (0.15, 0.67)	24.31	11.40	0.48 (0.21, 1.11)
Secondary outcomes						
Stroke – all types						
Events (%)	94 (3.1%)	6 (2.2%)		18 (3.7%)	6 (2.3%)	
Incidence rate‡	13.69	9.40	0.70 (0.31, 1.60)	16.80	9.77	0.60 (0.24, 1.50)
Myocardial infarction						
Events (%)	26 (0.8%)	-		1 (0.2%)	-	
Incidence rate‡	3.73	-	**	0.91	-	**
All-cause death						
Events (%)	131 (4.3%)	1 (0.4%)		8 (1.7%)	1 (0.4%)	
Incidence rate‡	18.71	1.54	0.08 (0.01, 0.59)	7.28	1.60	0.22 (0.03, 1.79)

Abbreviations: CI=confidence interval; DAPT=dual antiplatelet therapy; HR=hazard ratio; MI = myocardial infarction; SAPT=single antiplatelet therapy; PSM=propensity score matching
** Not estimated due to absent of event in the DAPT group.
‡Incidence rate denotes events/total person-years (per 100 person-years)

TABLE 4: Effectiveness outcome event rates for 1-year follow-up and hazard ratios of DAPT compared to SAPT

	Before PSM			After PSM		
	SAPT	DAPT	Crude HR (95& CI)	SAPT	DAPT	Crude HR (95& CI)
N	**3072**	**272**		**481**	**262**	
Primary outcome						
Composite endpoint of stroke, MI, or death						
No. of events (%)	359 (11.7%)	12 (4.4%)		42 (8.7%)	12 (4.6%)	
Incidence rate‡	23.47	6.89	0.32 (0.18, 0.58)	16.01	7.16	0.48 (0.25, 0.91)
Secondary outcomes						
Stroke – all types						
Events (%)	137 (4.5%)	6 (2.2%)		27 (5.6%)	6 (2.3%)	
Incidence rate‡	8.86	3.42	0.44 (0.19, 0.99)	10.27	3.55	0.38 (0.16, 0.92)
Myocardial infarction						
Events (%)	52 (1.7%)	2 (0.7%)		2 (0.4%)	2 (0.8%)	
Incidence rate‡	3.27	1.12	0.35 (0.08, 1.43)	0.73	1.16	**
All-cause death						
Events (%)	184 (5.9%)	4 (1.5%)		14 (2.9%)	4 (1.5%)	
Incidence rate‡	11.48	2.23	0.22 (0.08, 0.58)	5.11	2.31	0.48 (0.16, 1.45)

Abbreviations: CI=confidence interval; DAPT=dual antiplatelet therapy; HR=hazard ratio; MI = myocardial infarction; SAPT=single antiplatelet therapy; PSM=propensity score matching.
** Not estimated due to absent of event in the DAPT group.
‡Incidence rate denotes events/total person-years (per 100 person-years)

observed in those treated with DAPT (HR 0.38; 95% CI 0.16, 0.92). No differences between DAPT and SAPT were observed for other secondary outcomes.

Safety Outcome

Table 5 showed the risk of major bleeding among the study cohort. Only a few numbers of bleeding events were recorded during follow-up. PS-matched analysis showed no differences between DAPT and SAPT in the risk of bleeding at 90 days (HR 0.45; 95% CI 0.05, 4.01) and 1 year (HR 0.35; 95% CI 0.04, 2.96). Most of the bleeding events that occurred were during the first 90 days of follow-up.

DISCUSSION

In this retrospective cohort study of ischaemic stroke/TIA patients, there was a lower rate of the primary composite outcome of recurrent stroke, MI, or all-cause mortality for patients in the DAPT group than in the SAPT group, in which significant risk reduction associated with DAPT treatment was observed during the first year after discharge. All-cause

TABLE 5: Bleeding event rates at 90-day and 1-year follow-up

	Before PSM			After PSM		
	SAPT	**DAPT**	**Crude HR (95& CI)**	**SAPT**	**DAPT**	**Crude HR (95& CI)**
N	**3072**	**272**		**481**	**262**	
90-day						
Events (%)	33 (1.1%)	1 (0.4%)		4 (0.8%)	1 (0.4%)	
Incidence rate	4.75	1.55	0.34 (0.05, 2.46)	3.66	1.61	0.45 (0.05, 4.01)
1-year						
Events (%)	43 (1.4%)	1 (0.4%)		5 (1.0%)	1 (0.4%)	
Incidence rate	2.71	0.56	0.24 (0.03, 1.71)	1.84	0.58	0.35 (0.04, 2.96)

Abbreviations: CI=confidence interval; DAPT=dual antiplatelet therapy; HR=hazard ratio; SAPT=single antiplatelet therapy; PSM=propensity score matching

mortality was the major events (~50%) among the three outcomes while post-stroke MI was relatively rare. Bleeding rates were noted to be not significantly different between the two antiplatelet groups.

Less than 10% of patients from our study population were discharged on DAPT, which showed that a DAPT regimen was not widely used in the local clinical practice during this period. Over 90% of the DAPT group were on ASA-clopidogrel regimen, while other combinations were used less frequently. In this study, the number of patients in the DAPT group was lower than expected, especially when compared to other countries in which data from their stroke registries or cohort within a similar study period had approximately 30% to 45% of ischaemic stroke patients treated with DAPT (Borghol et al. 2020; Kim et al. 2019b; Xian et al. 2020). The low utilisation rate may occur for several reasons. Firstly, the combination of ASA-dipyridamole regimen is not widely used in Malaysia due to the unavailability of sustained-release dipyridamole locally (Malaysian Society of Neurosciences 2021). Secondly, the study population only included stroke patients diagnosed between 2014 and 2017 due to data availability. During this period, recommendations for DAPT for secondary stroke prevention have become better defined, with more evidence available to provide support for the effectiveness of DAPT that led to updates in guideline recommendations for early treatment with DAPT for patients with minor stroke or high-risk TIA (Powers et al. 2018; Hackam & Spence 2019). Yet, translation of evidence into real-world practice requires time while taking into account the benefit-risk profile for individual patients that may not be represented by average patients included in clinical trials. The present study comprised a cohort of patients with a first-ever documented stroke and it is likely that conventional treatment with SAPT is still preferred if the patients are likely to benefit from it, despite the emergence of new recommendations.

The trend of antiplatelet prescription patterns following publication of findings from key trials and guideline updates has been previously reported (Xian et al. 2020), in which DAPT use showed progressive increase over time in accordance with the latest recommendations. Similarly, in the present study, there was a pattern of increasing DAPT use over the 4 years, albeit at a lower rate.

In this study, our findings suggested the potential benefits of early treatment with DAPT in ischaemic stroke/TIA patients. Two major trials i.e. the CHANCE and POINT trials both involved patients with high-risk TIA and minor ischaemic stroke and demonstrated the superior efficacy of early treatment with DAPT over SAPT in reducing the risk of secondary events in the first 90 days (Johnston et al. 2018; Wang et al. 2013), with no changes in the risk-benefit ratio between the two groups within 1 year (Wang et al. 2015). Our study built upon the results of these trials to determine the antiplatelet treatment effect in our local population through observational analyses from multi-centre registries. The 90-day absolute risks of composite events in our study were 2.7% in DAPT and 5.4% in SAPT which was lower than that found in the CHANCE trial (8.4% versus 11.9%) and the more recent POINT trial (5.2% versus 6.6%). Although we did not find a significant association for the effectiveness outcome at 90 days, a similar trend of risk reduction was observed for DAPT compared to SAPT. The lower rates could potentially be explained by the small sample within our population with low event rates that resulted in a smaller effect size. However, our study showed a significant reduction in the composite endpoints with DAPT when compared to the SAPT group during 1-year follow up that was also consistent with the extended CHANCE trial which reported lower rates of combined vascular events for aspirin-clopidogrel than aspirin group (HR 0.78; 95% CI 0.65, 0.93) after 1-year (Wang et al. 2015). Similarly, Kim et al. (2019a) in a registry-based study showed a reduced risk of composite events associated with DAPT compared with SAPT during the first year after stroke. Despite the results between these trials and our current study were not strictly comparable owing to different study methods and population, our results indicated that favourable treatment benefits with DAPT over SAPT were similarly observed in the real-world practice among our local population in Malaysia.

DAPT is recommended based on the subtype of stroke (NIHSS score less than 4 or high-risk TIA) (Powers et al. 2018) or the presence of significant vascular stenosis (Chimowitz et al. 2011). The latter was not studied; however, patients of all ischaemic stroke or TIA types, regardless of severity, were included in our study. The broader patient population might have included groups more likely to either respond to therapy or are at increased risk for further vascular events, which might neutralise treatment effects. This was seen in several observational studies that assessed the effectiveness of antiplatelet therapy in patients whose

stroke characteristics were not limited as in the trials and found that DAPT did not reduce the risk of composite vascular events or stroke compared with SAPT (Borghol et al. 2020; Kim et al. 2019b). Furthermore, in our study there was a higher prevalence of risk factors in the DAPT group - a pattern that had been similarly observed in other studies of an observational nature (Barlas et al. 2018; Kim et al. 2019a). We had addressed these issues by applying analytical correction with propensity score matching. Yet, small event rates within our study population also limited further analysis by specific subgroups to further confirm our results. Nonetheless, our study population was predominantly Asian with multiethnic groups representative of the Malaysian population. The different ethnic communities by themselves were known to have differences in the prevalence of non-communicable diseases, risk factors, and genetic polymorphisms associated with antiplatelet resistance (Chan et al. 2015; Hasan et al. 2013; Teh et al. 2014). Therefore, our study provides valuable information on treatment strategies for this group of Asian population with multiethnicity, for comparison with studies previously conducted in other Asian and Western countries.

The use of DAPT for secondary prevention in stroke had been debated due to its association with a higher risk of bleeding complications than either of the antiplatelets alone (Diener et al. 2004; Bhatt et al. 2006; Benavente et al. 2012). While the CHANCE trial found a trend for increased bleeding risks in DAPT but with no significant difference compared to SAPT, the POINT trial found a significantly increased risk of major haemorrhage in the DAPT group which could be linked to the use of a higher loading dose and longer duration of DAPT administration (90 days in the POINT trial versus 21 days in the CHANCE trial) (Johnston et al. 2018; Tillman et al. 2019; Wang et al. 2013; Wang et al. 2015). In our study, the risk of major bleeding among patients in the DAPT group was not significantly different to those in the SAPT group during follow-up. Our results also showed that most of the bleeding events occurred within the first 90 days of follow-up, which was in accordance with other studies that reported a high early risk of bleeding associated with DAPT which declined over time (Hilkens et al. 2018). Nevertheless, bleeding events captured in the present study were based on admissions to hospitals and some events might be missed especially if no official diagnosis was made and not captured in medical records.

This observational study was conducted by pooling together data from several sources through data linkage to construct a longitudinal cohort and included a large number of stroke patients from major tertiary hospitals in Malaysia. Yet, the observational study design came with limitations that should be considered when interpreting the results of this study. Loss to follow-up was a limitation as this was a retrospective study based on available records. The choice of antiplatelet treatment and duration were not randomised and controlled.

In addition, the use of loading dose and inpatient treatment were not evaluated. Patients' adherence to medication was unknown and prescription records may not necessarily reflect actual consumption of medication by patients. Outcome events were solely based on a patient being hospitalised and it remained unidentified if it did not cause admissions to hospitals or if death is not registered to relevant authorities. Admissions to private hospitals were not included due to data availability. However, our study provided a good representative of the public sector and admissions to public hospitals comprised approximately 70% of total hospital admissions in the country (Ministry of Health Malaysia 2019). Lastly, although we used PS analysis to balance covariates between the two treatment groups, residual or unmeasured confounding cannot be excluded. Due to the small number of patients in our cohort who were DAPT users, PS matching resulted in a smaller number of patients in the analysis of the matched cohort. However, given the small sample size and the low prevalence of treatment, PS matching is considered a more robust approach than the traditional multivariate regression models and can yield correct estimations of treatment effects (Pirracchio et al. 2012). Nevertheless, further research in a larger population building on findings from this study is warranted to explore the treatment effect in greater depth.

CONCLUSION

In this study with a large representation of ischaemic stroke and TIA patients in Malaysia, we found that treatment with DAPT was associated with a lower risk of composite event and recurrent stroke within 1-year after discharge compared to SAPT. No significant difference between DAPT and SAPT in regards to the bleeding risk was observed. These findings suggested that important differences existed in the effectiveness of antiplatelet therapy when used individually or in combination for secondary prevention after an ischaemic stroke or TIA and with similar safety profiles. Although our results indicated favourable treatment outcomes with DAPT over SAPT, it should be applied judiciously in clinical practice with consideration of the strengths and limitations of this study. Further studies including broader population and larger-scale data are needed to strengthen the extent of the evidence and identify groups that could benefit the most from the more intensive antiplatelet therapy while balancing the bleeding risk.

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AUTHORS CONTRIBUTION

NAR, LWC, WYH, and SS conceived the study. NAR, LWC, WAWZ, ZAA, NNS, IL, MTL, SHLP, and WYH were involved in data acquisition and data collection. NAR analysed and interpreted the data. LWC, WAWZ, WYH, SS, ZAA, and IL interpreted the data. NAR wrote the initial draft of the manuscript. All authors revised the manuscript and approved the final manuscript for submission.

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