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Impact of the Additive Effect of Angiotensin-Converting Enzyme Inhibitors and/or Statins with Antiplatelet Medication on Mortality After Acute Ischaemic Stroke

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Abstract: There has been recent interest in combining antiplatelets, angiotensin-converting enzyme inhibitors (ACEIs) and statins in primary and secondary ischaemic stroke prevention. This observational study was performed to evaluate the impact of adding ACEIs and/or statins to antiplatelets on post-stroke in-hospital mortality. Ischaemic stroke patients attending a hospital in Malaysia over an 18-month period were evaluated. Patients were categorized according to their vital status at discharge. Data included demographic information, risk factors, clinical characteristics and previous medications with particular attention on antiplatelets, ACEIs and statins. In-hospital mortality was compared among patients who were not taking antiplatelets, ACEIs or statins before stroke onset *versus* those who were taking antiplatelets alone or in combination with either ACEIs, statins or both. Data analysis was performed using SPSS version 15. Overall, 637 patients met the study inclusion criteria. After controlling for the effects of confounders, adding ACEIs or statins to antiplatelets significantly decreased the incidence of death after stroke attack by 68% ($p = 0.036$) and 81% ($p = 0.010$), respectively, compared to patients on antiplatelets alone or none of these medications. Additionally, the addition of both ACEIs and statins to antiplatelet medication resulted in the highest reduction (by 94%) of the occurrence of death after stroke attack ($p < 0.001$). Our results suggest that adding ACEIs and/or statins to antiplatelets for patients at risk of developing stroke, either as a primary or as a secondary preventive regimen, was associated with a significant reduction in the incidence of mortality after ischaemic stroke than antiplatelets alone. These results might help reduce the rate of ischaemic stroke morbidity and mortality by enhancing the application of specific therapeutic and management strategies for patients at a high risk of acute stroke.

Stroke, a global health problem, is one of the leading causes of morbidity and mortality worldwide. Annually, about 16 million first-ever strokes occur worldwide, with a death toll of approximately 5.7 million people per year [1]. Over the past few decades, post-stroke mortality has declined in most developed countries. This beneficial trend was because of the better control of modifiable risk factors and improvements in medical care [2].

Previous studies resulted in conflicting data regarding the role of antiplatelet therapy, especially in the primary prevention of ischaemic stroke. Some studies reported that patients who suffer ischaemic stroke while taking aspirin have less severe strokes and more favourable outcomes [3,4]. However, others suggested that aspirin has no effect on stroke severity or its outcomes [5,6]. In the Women's Health study, a randomized primary prevention clinical trial, 10-year follow-up of 39,876 apparently healthy women health professionals to evaluate the benefits of aspirin in the primary prevention of stroke and cardiovascular diseases, was performed. The result showed that women taking aspirin experienced an overall 17% reduction in the risk of stroke [relative risk (RR) = 0.83; 95% confidence interval (CI) = 0.69–0.99; $p = 0.04$], mostly due to significant reductions in ischaemic stroke (RR = 0.76; 95% CI = 0.63–0.93; $p = 0.009$). In the subgroup analyses, aspirin significantly reduced the risk of ischaemic stroke among women aged 65 years or older. On the other hand, the trial found a non-significant increase in the risk of haemorrhagic stroke (RR = 1.24; 95% CI = 0.82–1.87; $p = 0.31$) [7]. As a secondary end-point, there was no significant difference between the groups in the risk of fatal stroke (RR = 1.04; 95% CI = 0.58–1.86; $p = 0.90$), but the aspirin group had a decreased risk of non-fatal strokes (RR = 0.81; 95% CI = 0.67–0.97; $p = 0.02$), as compared with the placebo group [7].

Angiotensin-converting enzyme inhibitors (ACEIs) and statins are being increasingly prescribed for ischaemic stroke prevention. Recent studies indicate that previous use of ACEIs and statins can reduce the incidence of ischaemic stroke in populations at risk [8,9] and that their use may be

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associated with less severe deficits and an improved functional outcome [10–12].

Most previous studies focused on the role of one preventive medication of antiplatelets, ACEIs or statins on ischaemic stroke outcomes. Recently, there has been an interest in combining these therapies for the primary and secondary prevention of ischaemic stroke [13].

What is the impact of the additive effect of ACEIs and/or statins with antiplatelet medication on in-hospital mortality? In our study, we hypothesized that the addition of ACEIs and/or statins to antiplatelet medication before ischaemic stroke attack might be associated with better outcomes, such as a reduction in the incidence of post-stroke in-hospital mortality. Therefore, we performed this observational study to evaluate the impact of adding ACEIs and/or statins to antiplatelet medication on in-hospital mortality and to identify the factors associated with post-stroke in-hospital mortality, including demographic factors, risk factors and clinical characteristics, in addition to previous medication.

Methodology

Patients, setting and study design.
We retrospectively reviewed the medical files of all acute ischaemic stroke patients who were admitted to a 1200-bed hospital located in northern Malaysia between 1 January 2008 and 30 June 2009. Before starting the study, permission for the use of patient clinical information was obtained from the local health authorities and medical ethics committee.

Patients were identified according to the International Classification of Diseases Tenth Revision (ICD-10). Using a computer-generated list obtained from the hospital record's office, patients with diagnostic codes I63.0–I63.9 (acute ischaemic stroke) were included in the study. Case verification was supplemented by records from medical wards and the intensive care unit. Acute ischaemic stroke was defined as an acute event of cerebrovascular origin causing focal or global neurological dysfunction lasting more than 24 hr and was confirmed by both clinical and radiographic means [14]. In addition, patients who were discharged against medical advice or who were referred to another hospital were excluded from the study.

The primary outcome of interest was post-stroke in-hospital mortality rates between patients with and without previous preventive antiplatelet medications and their combination with ACEIs and/or statins.

On the other hand, ischaemic stroke survivors were evaluated regarding their functional status at discharge. The Barthel Index (BI), one of the most frequently used scoring tools for assessing the functional status and the activities of daily living of stroke patients, was measured for ischaemic stroke survivors at discharge [15]. In the current study, a score of 75 or more was defined as a good functional status with mild or no dependency on essential personal care [16,17]. In addition, the impact of previous antiplatelets use and their combination with ACEIs and/or statins on improving the functional status of the survivors was also evaluated.

Demographic factors, risk factors and clinical characteristics.
The demographic data, clinical characteristics and risk factors were retrieved for each patient.

After completing the diagnostic evaluation, acute ischaemic stroke was classified according to the Oxfordshire Community Stroke Project (OCSP) classification system; this classification depends on the signs and symptoms that appear at the time of maximal deficit after the attack without referring to brain imaging findings. This classification includes total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), posterior circulation infarct (POCI) and unclassified types [18]. Also, this type of classification can predict functional recovery and death after the attack [19].

The Glasgow Coma Scale (GCS) is a measure of the level of consciousness. It is measured upon admission and is composed of independent observations of the three aspects of behaviour of eye opening and motor and verbal responsiveness on a scale ranging from 3 (most severe cases) to 15 (highly conscious cases). In our study, the GCS was divided into three categories: minor (total score ≥ 13), moderate (total score 9–12) and severe (total score ≤ 8) [20].

The main risk factors included were hypertension [21], diabetes mellitus (DM) [22], dyslipidaemia [23], atrial fibrillation (AF), ischaemic heart disease [24], renal impairment [25], heart failure (HF) and previous stroke or transient ischaemic attack (TIA). Furthermore, vital signs at presentation, including blood pressure, body temperature and fasting or random blood glucose levels, were included in the analysis.

Previous medications.
All medications that were taken prior to the current stroke with particular attention on antiplatelets, ACEIs and statins were assessed. For a better evaluation of the impact of antiplatelet use either alone or with the addition of ACEIs and/or statins, we excluded patients who were on ACEIs alone, statins alone or ACEIs + statins before the current attack. In addition, as few patients were using angiotensin II receptor blockers (ARBs) and none were on ACEIs, these patients were considered as ACEI-treated patients for the purposes of statistical analysis.

Statistical analysis.
Data were entered and analysed using the Statistical Package for Social Sciences program version 15 (SPSS; SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as frequencies (%) and continuous variables as means ± standard deviations (S.D.). Variables that were not normally distributed were expressed as medians (lower–upper quartiles).

The patients included were categorized according to the vital status at discharge, and the survivor patients according to the functional status at discharge. Univariate statistics were used to determine the relationships between

demographic factors, risk factors, clinical characteristics and previous medications with in-hospital mortality.

Additionally, univariate analysis was used to study the impact of previous antiplatelet use alone *versus* the additive effect of ACEIs and/or statins with antiplatelet medication on ischaemic stroke outcome.

The chi-square or Fisher's exact tests were used, as appropriate, to test for significance between categorical variables. An independent Student's *t*-test was used to compare the means of continuous variables. If the assumptions of equality of variance and normality were not met, the Mann–Whitney *U*-test was performed where appropriate. A *p*-value of <0.05 was considered significant.

To prove a significant impact of the previous use of preventive medications on the incidence of in-hospital mortality and functional status, and to control for the possible effect of any candidate confounding factors and their potential interactions with antiplatelet medication and its combination results, all of the significant variables in the univariate analysis were included in the binary logistic regression model.

The proportion of patients who died during hospitalization or discharged with good outcome was expressed as a prevalence rate with a 95% CI. The association between dead cases and the variables of interest was evaluated by calculating the odds ratio (OR) with the corresponding 95% CI.

Results

Patient characteristics, risk factors and clinical characteristics. During the study period, 890 patients were admitted with a diagnosis of acute ischaemic stroke. Of these, 36 patients were excluded, 22 patients were discharged against medical advice and 14 were referred to another hospital. For the purpose of the study, of the remaining 854 patients, we excluded 217 patients. Of these, 95 patients were on ACEIs alone, 36 patients were on statins alone and 86 patients were on ACEIs + statins before the current attack. Therefore, 637 patients met our inclusion criteria (fig. 1).

Table 1 illustrates the univariate analysis of the demographic factors, risk factors, clinical characteristics and vital signs on admission of the ischaemic stroke patients according to their vital status at discharge.

The mean age of the patients was 65.7 ± 12.7 years; and 377 (59.2%) patients were men. Moreover, 424 (66.6%) patients had had their first attack, while the remaining 213 (33.4%) had had a previous stroke or TIA.

Of the 637 patients included, 100 (15.7%) died during hospitalization. Patients who died after the stroke attack were significantly older [OR = 1.03; 95% CI = (1.02–1.05; $p < 0.001$)]. In addition, in-hospital mortality occurred significantly more often among diabetic patients (OR = 1.8; 95% CI = 1.2–2.8; $p = 0.008$) and patients with AF (OR = 3.1; 95% CI = 1.6–5.9; $p < 0.001$), renal impairment (OR = 4.8; 95% CI = 2.9–7.9; $p < 0.001$) and HF (OR = 9.3; 95% CI = 2.9–18.9; $p < 0.001$).

Considering TACI stroke subtype as a reference, patients diagnosed with PACI (OR = 0.21; CI = 0.10–0.42; $p < 0.001$) or LACI (OR = 0.05; CI = 0.02–0.11; $p < 0.001$) were significantly having higher chance to survive after stroke attack. In addition, patients admitted with moderate (OR = 14.5; CI = 7.2–22.3; $p < 0.001$) or severe (OR = 55.7; CI = 27.2–85.2; $p < 0.001$) GCS had a significantly higher risk of death compared to patients with minor GCS.

Furthermore, elevated body temperature and blood glucose level were positively associated with in-hospital mortality (OR = 7.2; 95% CI = 4.3–11.9; $p < 0.001$) and (OR = 2.5; 95% CI = 1.6–3.9; $p < 0.001$), respectively. And patients who develop at least one complication post-stroke are likely to die after stroke attack (OR = 3.9; 95% CI = 2.2–6.9; $p < 0.001$).

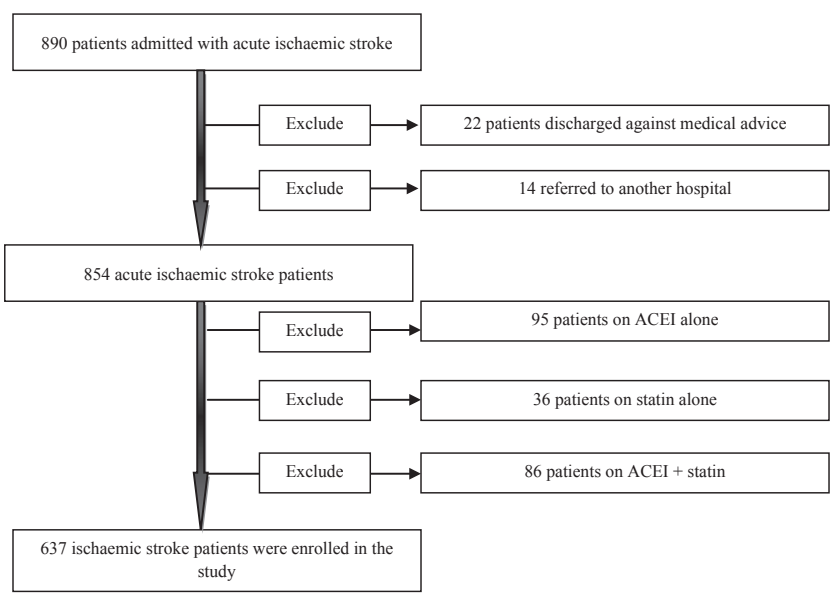

Fig. 1. Flow chart describing the inclusion criteria of ischaemic stroke patients in the study.

Table 1.
Patient demographic and clinical characteristics on admission by categories according to vital status at discharge (N = 637).

Variable	Total N (%) (N = 637)	Alive N (%) (N = 537)	Dead N (%) (N = 100)	Odds ratio with 95% CI	*p*-value
Age (year)					
Mean ± S.D.	65.7 ± 12.7	64.8 ± 12.8	70.2 ± 11.2	1.03 (1.02–1.05)	0.000[1]
Gender					
Male	377 (59.2)	322 (60.0)	55 (55.0)	1	0.354[2]
Female	260 (40.8)	215 (40.0)	45 (45.0)	1.2 (0.8–1.9)	
Ethnicity					
Malay	183 (28.8)	156 (29.0)	27 (27.0)	1	
Chinese	350 (54.9)	291 (54.2)	59 (59.0)	1.2 (0.7–1.9)	0.531[2]
Indian	93 (14.6)	80 (14.9)	13 (13.0)	0.9 (0.5–1.9)	0.863
Other	11 (1.7)	10 (1.9)	1 (1.0)	0.6 (0.1–4.7)	0.608
Stroke event					
First ever	424 (66.6)	351 (65.4)	73 (73.0)	1	0.137[2]
Recurrent	213 (33.4)	186 (34.6)	27 (27.0)	0.7 (0.4–1.1)	
OCSP subtypes					
TACI	56 (8.8)	29 (5.4)	27 (27.0)	1	
PACI	146 (22.9)	122 (22.7)	24 (24.0)	0.21 (0.10–0.42)	0.000[2]
LACI	287 (45.1)	273 (50.8)	14 (14.0)	0.05 (0.02–0.11)	0.000
POCI	61 (9.5)	40 (7.5)	21 (21.0)	0.56 (0.27–1.19)	0.131
Unclassified	87 (13.7)	73 (13.6)	14 (14.0)	0.21 (0.09–0.45)	0.000
GCS					
Minor	433 (68.0)	421 (78.4)	12 (12.0)	1	
Moderate	116 (18.2)	82 (15.3)	34 (34.0)	14.5 (7.2–22.3)	0.000[2]
Severe	88 (13.8)	34 (6.3)	54 (54.0)	55.7 (27.2–85.2)	0.000
Onset and arrival time					
Median (Q1–Q3)	12 (5.0–48.0)	14 (5.0–48.0)	7 (4.0–35.3)	–	0.161[3]
Risk factors					
Hypertension	521 (81.8)	437 (81.4)	84 (84.0)	1.2 (0.7–2.1)	0.533[2]
DM	292 (45.8)	234 (43.6)	58 (58.0)	1.8 (1.2–2.8)	0.008[2]
Dyslipidaemia	215 (33.8)	187 (34.8)	28 (28.0)	0.7 (0.4–1.2)	0.186[2]
AF	47 (7.4)	31 (5.8)	16 (16.0)	3.1 (1.6–5.9)	0.000[2]
IHD	130 (20.4)	108 (20.1)	22 (22.0)	1.1 (0.7–1.9)	0.667[2]
Renal impairment	92 (14.4)	56 (10.4)	36 (36.0)	4.8 (2.9–7.9)	0.000[2]
Valvular heart disease	11 (1.7)	9 (1.7)	2 (2.0)	1.2 (0.3–2.6)	0.819[4]
Heart failure	13 (2.0)	5 (0.9)	8 (8.0)	9.3 (2.9–18.9)	0.000[4]
Vital signs on admission					
BP (high)	117 (18.4)	101 (18.8)	16 (16.0)	0.8 (0.5–1.5)	0.505[2]
Body temperature (high)	83 (13.0)	44 (8.2)	39 (39.0)	7.2 (4.3–11.9)	0.000[2]
FBG/RBG (high)	300 (47.1)	234 (43.6)	66 (66.0)	2.5 (1.6–3.9)	0.000[2]
Complication	402 (63.1)	317 (59.0)	85 (85.0)	3.9 (2.2–6.9)	0.000[2]

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; FBG, fasting blood glucose; IHD, ischaemic heart disease; GCS, Glasgow Coma Scale; LACI, lacunar infarct; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; Q1–Q3, lower quartile to upper quartile; RBG, random blood glucose; S.D., standard deviation; TACI, total anterior circulation infarct.
[1]Significance of differences estimated with Student's *t*-test.
[2]Significance of differences estimated with the chi-square test.
[3]Significance of differences estimated with the Mann–Whitney *U*-test.
[4]Significance of differences estimated with Fisher's exact test.

Medications used and in-hospital mortality.
Table 2 summarizes the univariate analysis of medications that were used prior to hospitalization. It was shown that none of the previous antihypertensive agents or antidiabetics had any positive effect on reducing the incidence of death after stroke attack.

In-hospital mortality rate was significantly lower among previous users of antiplatelets. These users were on antiplatelets alone or with ACEIs and/or statins. Among the 100 dead cases, 24 (24.0%) were on antiplatelet medication prior to admission compared to 76 (76.0%) who were not on antiplatelets before the current attack (OR = 0.2; 95% CI = 0.1–0.3; $p < 0.001$).

Impact of the additive effect of ACEIs and/or statin with antiplatelet medication on in-hospital mortality.
Of the 345 patients who had used antiplatelet medication prior to stroke attack, 52 (8.2%) were on antiplatelets alone, 85 (13.3%) took an antiplatelet + ACEI, 66 (10.4%) took an antiplatelet + statin and 142 (22.3%) took ACEIs and statins

Table 2.
Previous medications given by categories according to vital status at discharge (N = 637).

Variable	Total N (%) (N = 637)	Alive N (%) (N = 537)	Dead N (%) (N = 100)	Odds ratio with 95% CI	*p*-value
β-Blockers	264 (41.4)	221 (41.2)	43 (43.0)	1.1 (0.7–1.7)	0.731[1]
CCB	115 (18.1)	96 (17.9)	19 (19.0)	1.1 (0.6–1.9)	0.789[1]
Diuretic	75 (11.8)	64 (11.9)	11 (11.0)	0.9 (0.5–1.8)	0.794[1]
α-Blockers	17 (2.7)	16 (3.0)	1 (1.0)	0.3 (0.1–1.9)	0.259[2]
Anticoagulants	9 (1.4)	7 (1.3)	2 (2.0)	1.5 (0.3–4.5)	0.588[2]
Antidiabetic agents	197 (30.9)	167 (31.1)	30 (30.0)	0.9 (0.6–1.5)	0.827[1]

CCB, calcium channel blocker; CI, confidence interval.
[1]Significance of differences estimated with the chi-square test.
[2]Significance of differences estimated with Fisher's exact test.

Table 3.
Previous antiplatelet and its combinations given by categories according to vital status at discharge (N = 637).

Variable	Total N (%) (N = 637)	Alive N (%) (N = 537)	Dead N (%) (N = 100)	Odds ratio with 95% CI	*p*-value
None	292 (45.8)	216 (40.2)	76 (76.0)	1	
AP alone	52 (8.2)	44 (8.2)	8 (8.0)	0.51 (0.23–1.15)	0.105[1]
AP + ACEI	85 (13.3)	79 (14.7)	6 (6.0)	0.22 (0.09–0.51)	0.001
AP + statin	66 (10.4)	61 (11.4)	5 (5.0)	0.23 (0.09–0.60)	0.003
AP + ACEI + statin	142 (22.3)	137 (25.5)	5 (5.0)	0.10 (0.04–0.26)	0.000

ACEI, angiotensin-converting enzyme inhibitor; AP, antiplatelet; CI, confidence interval.
[1]Significance of differences estimated with the chi-square test.

in combination with antiplatelet medication prior to ischaemic stroke attack (table 3).

In table 3, which considers the patients who took no preventive therapy as a reference, the univariate analysis shows that the antiplatelet medication alone group did not significantly differ from the reference group on the reduction in the incidence of in-hospital mortality (OR = 0.51; 95% CI of 0.23–1.15; $p = 0.105$). Furthermore, adding ACEIs and/or statins to antiplatelet medication gave a significant protective effect by reducing the rate of mortality after stroke attack (OR = 0.22; 95% CI of 0.09–0.51; $p = 0.001$) and (OR = 0.23; 95% CI of 0.09–0.60; $p = 0.003$), respectively.

Does the preventive impact of adding ACEIs and/or statins to antiplatelet medication remain after controlling for other possible confounding variables?

To prove the significant reduction in the incidence of in-hospital mortality, and to control for the effects of any confounders that may have affected the results of antiplatelet medication and its combinations, all of the significant variables in the univariate analysis were included in the binary logistic regression model (table 4).

A test of the full model with all of the predictors against a constant-only model was statistically reliable: $\chi^2 = 275.5$, df = 18 and $p < 0.001$, indicating that the predictors, as a set, reliably distinguished between alive and dead cases. Using the Cox and Snell R^2 measure, the logistic regression resulted in a model accounting for 35.1% of the variance ($R^2 = 0.351$), and as much as 60.5% of the variance based on these variables (Nagelkerke $R^2 = 0.605$). The full model correctly classified 96.3% of the cases alive at discharge and 63.0% of the cases dead during hospitalization, resulting in an overall prediction rate of 91.1%.

Regarding the impact of the additive effect of ACEIs and/or statins with antiplatelet medication after controlling for other variables, the addition of ACEIs to antiplatelet medication significantly decreased the rate of death after stroke attack by 68% (OR = 0.32; 95% CI = 0.09–0.87; $p = 0.036$). Moreover, the addition of statins to antiplatelets as a preventive combination prior to stroke attack significantly reduced the occurrence of mortality by 81% after attack (OR = 0.19; 95% CI = 0.05–0.67; $p = 0.010$). Additionally, the addition of both ACEIs and statins to antiplatelet medication significantly reduced the incidence of mortality after stroke attack by 94% (OR = 0.06; 95% CI = 0.02–0.21; $p < 0.001$) (table 4).

In addition to the positive effect of preventive medication combination on the reduction in mortality after stroke, the binary logistic regression (table 4) identifies the other predictors for the incidence of post-stroke in-hospital mortality.

At time of admission, moderate and severe GCS were independently associated with post-stroke in-hospital mortality (OR = 9.52; 95% CI = 3.69–15.53; $p < 0.001$ and OR = 34.43; 95% CI = 12.76–56.88; $p < 0.001$, respectively). Moreover, the odds of in-hospital mortality increase by 2.43 times among patients admitted with higher body temperature (95% CI = 1.14–5.14; $p = 0.021$). Furthermore, DM (OR = 2.22; 95% CI = 1.08–4.58; $p = 0.031$), AF (OR = 3.65; 95% CI = 1.38–5.67; $p = 0.009$), renal impairment (OR = 4.29; 95% CI = 2.01–7.19; $p < 0.001$) and HF (OR = 21.38; 95%

Table 4.
Independent factors associated with in-hospital mortality using binary logistic regression analysis.

Variables	β	S.E.	Wald	Sig.	Odds ratio (95% CI)
Previous medications					
None			23.85		1
AP alone	−0.45	0.65	0.48	0.490	0.64 (0.18–2.29)
AP + ACEI	−1.15	0.62	3.44	0.036	0.32 (0.09–0.87)
AP + statin	−1.66	0.64	6.71	0.010	0.19 (0.05–0.67)
AP + ACEI + statin	−2.85	0.65	19.08	0.000	0.06 (0.02–0.21)
Age	−0.01	0.01	0.21	0.649	0.99 (0.97–1.02)
OCSP stroke classification					
TACI			8.48		1
PACI	−0.17	0.48	0.13	0.720	0.84 (0.33–2.14)
LACI	0.01	0.56	0.01	0.982	1.01 (0.34–3.06)
POCI	1.27	0.58	4.85	0.028	3.55 (1.15–5.99)
Unclassified OCSP	−0.04	0.57	0.01	0.941	0.96 (0.32–2.91)
GCS classification					
Minor			48.94		1
Moderate	2.25	0.48	21.76	0.000	9.52 (3.69–15.53)
Severe	3.56	0.51	48.86	0.000	34.43 (12.76–56.88)
Risk factors					
Diabetes mellitus	0.79	0.37	4.66	0.031	2.22 (1.08–4.58)
Atrial fibrillation	1.29	0.49	6.76	0.009	3.65 (1.38–5.67)
Renal impairment	1.48	0.39	14.04	0.000	4.29 (2.01–7.19)
Heart failure	3.06	0.99	9.41	0.002	21.38 (3.02–40.34)
Vital signs on admission					
Body temperature	0.89	0.38	5.34	0.021	2.43 (1.14–5.14)
FBG/RBG	0.46	0.36	1.58	0.208	1.58 (0.78–3.22)
Complications	−0.02	0.45	0.01	0.957	0.98 (0.40–2.38)

ACEI, angiotensin-converting enzyme inhibitor; AP, antiplatelet; β, the coefficient of the predictor variables; CI, confidence interval; FBG, fasting blood glucose; GCS, Glasgow Coma Scale; LACI, lacunar infarct; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; RBG, random blood glucose; S.E, standard error; TACI, total anterior circulation infarct.

CI = 3.02–40.34; $p = 0.002$) are considered among the independent predictors for in-hospital mortality among ischaemic stroke patients.

On the other hand, ischaemic stroke survivors were assessed for their functional status at discharge. Considering patients who had not taken any of the three preventive medications as a reference group, the results showed that an antiplatelet treatment alone and an antiplatelet with an ACEI and/or statin had a significant impact on improving the functional status of patients at discharge. Moreover, the odds of a good functional status at discharge were four times higher (95% CI = 3.48–10.53; p-value < 0.001), 4.7 times higher (95% CI = 2.36–9.51; p-value < 0.001) and 5.4 times higher (95% CI = 3.38–13.30; p-value < 0.001) in patients who were treated with an antiplatelet alone, an antiplatelet with a statin and an antiplatelet with an ACEI, respectively. Moreover, patients who were previously treated with an ACEI and statin, together with an antiplatelet, had the highest odds of being discharged with a good functional status, as measured by BI ≥ 75 (OR = 5.8; 95% CI = 2.68–14.98; p-value < 0.001).

Discussion

The in-hospital mortality rate was significantly lower among the group of patients who used antiplatelet medication before stroke attack compared to non-antiplatelet users. However, this group of antiplatelet users were on antiplatelets alone or antiplatelets with ACEIs and/or statins. Therefore, a comparison between the different additive regimens of ACEIs and/or statins with antiplatelets and their effects on the post-stroke mortality rate was performed.

After controlling for other confounders that may have affected the results of previous medication regimens, the binary logistic regression result showed that adding ACEIs to antiplatelet medication significantly decreased the mortality rate after stroke attack by 68%, statins to antiplatelets by 81%, and the addition of both ACEIs and statins to antiplatelets by 94%. However, antiplatelet medication alone did not significantly differ from the reference group in reducing the rate of post-stroke in-hospital mortality.

Aspirin and other antiplatelet agents are effective in secondary prevention after stroke or TIA, but their effectiveness for the primary prevention of stroke is controversial [26]. A meta-analysis of randomized trials comparing aspirin with a placebo in the primary prevention of stroke found that aspirin reduced the frequency of all cardiovascular events, mainly because of significant reductions in coronary events, but not ischaemic stroke [27]. Also, recent studies failed to show a significant association between the previous use of antiplatelet medication and initial stroke severity or early and 6-month stroke outcomes [28,29]. However, significant reduction in the

RR of stroke, mostly because of significant reductions in ischaemic stroke was the result of the Women's Health trial [7].

To the best of our knowledge, no trials have focused on the impact of medication combinations in acute ischaemic stroke. In 2006, an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) proposed the potential synergistic effect of atorvastatin and amlodipine in reducing cardiovascular events, but not stroke [30]. Moreover, another synergistic effect between the combination of ARB and statins was suggested in cardiovascular problems management, indicating a relationship between hypertension and dyslipidaemia [31].

Our results are supported by a recent observational study by Kumar *et al.* who concluded that the pre-stroke use of antiplatelets + ACEIs + statins may result in an additive reduction in stroke severity as measured by the NIH Stroke Scale (NIHSS) and the volume of ischaemic tissue at risk compared to patients on antiplatelet medication alone or patients who were on no previous medications [13].

In the current study, ischaemic stroke survivors who previously used an antiplatelet, ACEI and statin in combination may have an additive reduction in the clinical severity of their ischaemic stroke, which may be translated into the highest percentage of survivors being discharged with good functional status as measured by BI ≥ 75. However, in a previous study, a larger but insignificant percentage of patients on triple therapy showed minor disabilities at discharge according to the modified Rankin Scale (mRS) [13]. Another study that included any antihypertensive class together with antiplatelets and statins found that this combination was associated with a better functional outcome after stroke [29]. However, it was found that the previous use of any of these medications, either alone or in combination, did not produce a significant effect on stroke severity [29].

In the current study, we found no significant intergroup difference between patients who died and those who lived regarding the other medications, suggesting that the added beneficial effect of the combined regimen in our patients was unlikely to be related to other concomitant treatments.

The favourable additive effect of the ACEIs and/or statins to the antiplatelet medication was most likely the result of their multimodal actions.

The mechanisms by which antiplatelet medications might decrease stroke severity include the stabilization of plaques and a decrease in platelet aggregation, thus reducing the size and frequency of emboli [32]. Furthermore, aspirin may have additional benefits on stroke severity through anti-inflammatory, anti-pyretic and neuroprotective mechanisms [33]. ACEI might provide neuroprotection by blocking angiotensin II-mediated endothelial dysfunction, lipid peroxidation, oxidative stress and vascular smooth muscle intracellular calcium accumulation and hypertrophy [34,35]. Additionally, ACEIs may help to maintain the homoeostatic balance between fibrinolytic and pro-coagulant factors [36], and they may enhance cerebral blood flow and reduce stroke severity [37]. In addition, studies have indicated that statins have multiple effects beyond simply lowering the cholesterol level [38]. Some of these effects might be neuroprotective [39]. In addition, statins might interfere with platelet aggregation or have anti-inflammatory, anti-oxidative and anti-apoptotic properties [40], and they could enhance blood flow to the ischaemic brain [40]. In the current study, these therapies may act synergistically to attenuate ischaemic injury and reducing stroke severity by enhancing blood flow in the cerebral microcirculation within the ischaemic area.

To the best of our knowledge, this study is the first of its kind in this area and is among only a very few recent studies that discuss the combined regimen of antiplatelets, ACEIs and statins and their impact on stroke outcome. However, there were some limitations to this study, including its retrospective nature. Also, we were unable to analyse the duration that the medication was used prior to the current attack. Mortality was only assessed during the in-patient period without further evaluation after discharge. In addition, stroke infarct volume was not measured from magnetic resonance imaging (MRI) scan image.

Conclusion and Recommendations

Our results suggest that the addition of ACEIs and/or statins to antiplatelet medication for patients at risk of developing stroke, either as a primary or as a secondary preventive regimen, was associated with a significant reduction in the incidence of mortality after ischaemic stroke compared to the use of antiplatelet medication alone. The triple combination of antiplatelets, ACEIs and statins resulted in the highest reduction in mortality rate after stroke attack. The results of this study might help reduce the rate of morbidity and mortality after ischaemic stroke by enhancing the application of specific therapeutic and management strategies for patients at a high risk of acute stroke.

Our findings need to be prospectively validated in randomized studies to confirm the effectiveness of these preventative medications on mortality and functional outcomes after stroke.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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