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ORIGINAL RESEARCH

Antiplatelet Treatment Patterns and Outcomes for Secondary Stroke Prevention in the United Kingdom

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ABSTRACT

Introduction: Stroke is a leading cause of death and disability worldwide. Antiplatelet therapies are recommended to reduce the risk of recurrent stroke in patients with ischemic stroke/transient ischemic attack (IS/TIA). This study evaluated outpatient antiplatelet treatment patterns and outcomes for secondary stroke prevention (SSP) among UK adults without atrial fibrillation who were hospitalized for IS/TIA.

Methods: This retrospective observational study utilized data from the UK Clinical Practice Research Datalink linked with Hospital Episode Statistics data (01/01/2011–30/06/2019). Treatment patterns included type and duration of treatments. Treatment outcomes included IS, myocardial infarction, major bleeding, and cardiovascular-related and all-cause mortality. Descriptive statistics were reported.

Results: Of 9270 patients, 13.9% (1292) might not receive antithrombotic therapy within 90 days of hospital discharge. Of 7978 patients who received antiplatelet therapies, most used clopidogrel (74.8%) or aspirin (16.7%) single antiplatelet therapy and clopidogrel + aspirin dual antiplatelet therapy (DAPT, 5.9%). At 1-year post-hospitalization, 36.9, 43.3, and 35.1% of those receiving these treatments discontinued them, respectively, and of the patients initiating DAPT, 62.3% switched to single antiplatelet therapy. At 1-year post-discharge, the incidence rate (per 100 person-years) of IS, myocardial infarction, major bleeding, cardiovascular-related mortality, and all-cause mortality among the treated were 6.5, 0.7, 4.1, 5.0, and 7.3, respectively, and among the untreated were 14.9, 0.7, 8.6, 28.1, and 39.8, respectively.

Conclusions: In the United Kingdom, 13.9% of patients hospitalized for stroke might not have any antiplatelet treatment to prevent secondary stroke; among the treated, clopidogrel, aspirin, and DAPT were commonly used. These study findings suggest that improved anti-thrombotic therapies for long-term SSP treatment are needed, which may lead to higher treatment and persistence rates and, therefore, improved outcomes in this population.

Keywords: Antiplatelet therapy; Drug utilization; Stroke; Thrombosis

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Key Summary Points

Why carry out this study?

Antiplatelet therapies are recommended for secondary stroke prevention (SSP) in patients with ischemic stroke/transient ischemic attack (IS/TIA), taking into account the benefit–risk tradeoff (reduction in risk of recurrent stroke and risk of bleeding associated with antiplatelet use) as assessed by physicians.

This study evaluated outpatient antiplatelet treatment patterns and outcomes for SSP among UK adults without atrial fibrillation who were hospitalized for IS/TIA.

What was learned from the study?

In the UK, > 80% of patients who are at risk of recurrent stroke receive treatment and of these, 74.8% receive clopidogrel, followed by aspirin (16.7%), their combination (5.9%), and other treatments (2.6%). Despite the recommendation of long-term use of antiplatelets for SSP treatment, > 30% of the treated patients discontinue their antiplatelet therapy after 1 year and > 49% discontinue after 2 years.

Improved anti-thrombotic therapies are needed to improve persistence and outcomes of the long-term SSP treatment.

INTRODUCTION

Stroke is the second leading cause of death worldwide; it was responsible for 143 million disability-adjusted life-years and 6.55 million deaths in 2019 [1] and accounts for 3–4% of total Western health care expenditure [2]. Because of the aging population and improved survival rates, the number of patients living with stroke in the European Union is projected to increase by 27% between 2017 and 2047, amounting to an additional 2.58 million prevalent cases [3]. In the United Kingdom, 100,000 people have strokes each year and there are as many as 1.3 million stroke survivors [4]. UK estimates suggest a mean yearly cost of £45,409 associated with new-onset stroke in the first year and £24,778 in subsequent years, amounting to an aggregate of £26 billion per year, including £8.6 billion for National Health Service and social care [5].

Estimates of the risk of recurrent stroke within 90 days of an ischemic stroke (IS) or transient ischemic attack (TIA) range from 0.6 to 20.6% [6–10]. Antiplatelet therapies, such as aspirin and clopidogrel, are widely recommended for secondary stroke prevention (SSP) [11–14]. Also, data from the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) study suggested a synergistic benefit associated with the combined use of both agents (termed dual antiplatelet therapy [DAPT]) [15]. Secondary analyses and meta-analyses of trial data also highlighted the importance of evaluating net clinical benefit and optimizing the benefit–risk profile in antiplatelet treatment decisions [15–17]. Understanding the real-world implications of antiplatelet therapy for SSP is also critical. Although studies have assessed the relative safety and effectiveness of aspirin versus clopidogrel for SSP [18–20], international guidelines vary by duration, dose, and treatment type. For example, the UK National Institute for Health and Care Excellence (NICE) guidelines favor clopidogrel over others and combined aspirin and dipyridamole over aspirin, whereas most guidelines consider all three as equivalent options [11, 13]. Currently, there is a lack of real-world data on SSP in diverse patient populations. We have therefore evaluated treatment patterns and outcomes in patients without atrial fibrillation (AF) receiving antiplatelet therapy for SSP following IS or TIA using real-world data from the UK Clinical Practice Research Datalink (CPRD).

METHODS

Study Design

This was a retrospective, observational study of treatment patterns and outcomes in hospitalized patients with primary IS or TIA without AF. Data were obtained from the CPRD linked with Hospital Episode Statistics (HES) Admitted Patient Care (APC) and Office for National Statistics (ONS) mortality data. The CPRD is a primary care database that includes longitudinal data from general practices and comprises a patient population that is generally considered representative of the UK population.

Participants

The index date for each patient was defined as the date of the first hospitalization for IS or TIA, occurring between January 1, 2012 and March 31, 2019 (the index identification period). The patients were required to have a 12-month baseline period before the index date (baseline period). Adult patients (aged $\geq$ 18 years) with one or more primary diagnosis of IS or TIA in the inpatient setting during the index period were included. Patients were excluded if they had a diagnosis of AF at any time from the baseline period until 30 days following discharge or a diagnosis of IS during the baseline period (defined as the 12 months prior to the index date). Patients with any diagnosis of hemorrhagic stroke or traumatic hemorrhage at or prior to their index date or with a prescription for an oral anticoagulant at any time during the baseline period or within 90 days post-discharge were also excluded. Patients who died during hospitalization and those with zero follow-up days were also excluded. Patients were further categorized as treated and untreated. For the treated patients, the index treatment was defined as the first antiplatelet prescription for SSP in CPRD post-index date and within 90 days post-discharge. Clinical outcomes were measured following discharge for both cohorts.

Data Collection

The study was conducted on the data generated between January 1, 2011 and June 30, 2019 (Fig. 1). All patients were required to have $\geq$ 12 months of continuous CPRD and HES coverage prior to the index date (baseline period).

For the analysis of treatment patterns, patients were followed from the time of their index treatment to the earliest of end of enrollment, study completion, discontinuation, or death. For the analysis of treatment outcomes, patients were followed from day 1 post-discharge to the earliest of end of enrollment, study completion, death, or 30 days after treatment discontinuation. Treatment patterns and clinical outcomes were assessed at 3, 6, 12, 24, and 36 months post-discharge. For the untreated cohort, the follow-up is defined as day 1 post-discharge until earliest of end of enrollment, study completion, or death.

Assessments

The primary objective was to evaluate antiplatelet treatment patterns after the first hospitalization for IS or TIA. Evaluation of treatment patterns included the type of treatment (i.e., single antiplatelet therapy [SAPT], DAPT, and no treatment), duration, discontinuation, and switch. The secondary objective was to describe the post-treatment incidence rates of IS, myocardial infarction (MI), major bleeding (defined based on primary diagnosis of hospitalization records, cause of death, and transfusion records [for major bleeding only]), mortality (cardiovascular-related, all-cause), and major adverse cardiac event (MACE) 1 (IS, MI, or cardiovascular-related mortality) or MACE 2 (overall stroke, MI, or all-cause mortality).

Analyses were stratified according to treatment with clopidogrel SAPT, aspirin SAPT, clopidogrel + aspirin DAPT (patients who initiated the two antiplatelet agents on the same day), or no treatment. The stratification was determined by the index prescription record, if available. The no treatment cohort included

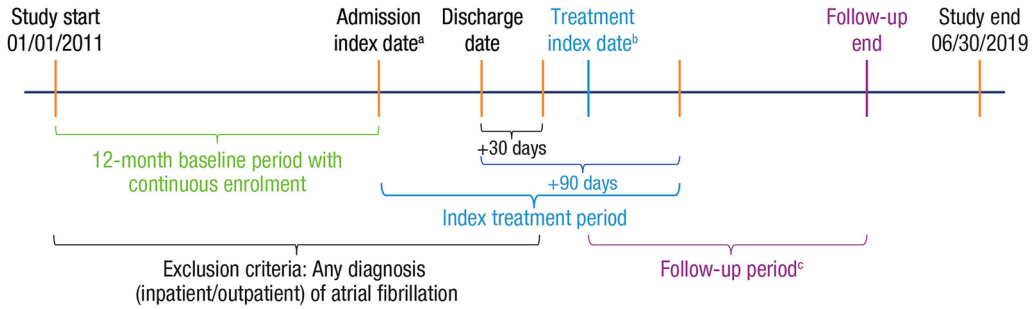


Fig. 1 Study design. *IS* ischemic stroke, *TIA* transient ischemic attack. [a]First hospitalization with principal diagnosis of IS or TIA between January 1, 2012 and March 31, 2019. [b]First antiplatelet treatment. [c]Any time from treatment index date until minimum of enrollment end, study end, discontinuation, or death

patients with no antithrombotic prescription (i.e., no antiplatelet and/or no anticoagulant [apixaban, rivaroxaban, dabigatran, edoxaban, warfarin]) from their index date to 90 days post-discharge. Antiplatelet therapy was defined in the CPRD as aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, or aspirin + dipyridamole (Aggrenox®).

Statistical Analyses

Descriptive statistics were applied across the study, including baseline characteristics, treatment patterns, and clinical outcomes. Baseline patient characteristics were summarized using frequencies and percentages for categorical values; means and standard deviations were used for continuous variables and to report treatment patterns. Clinical outcomes were reported in incidence rates. Only the first event of each type during the follow-up period was examined.

Ethical Approval

This article had been approved by the Independent Scientific Advisory Committee (ISAC), with the reference number ISAC19_240R. Although this study does not involve primary data collection from human participants, it was performed in accordance with the ethical principles set forth in the Helsinki Declaration of 1964 and its later amendments. Given that this study was based on retrospective analyses of secondary databases without enrollment of patients, all data were anonymized and de-identified prior to analysis.

RESULTS

Patient Characteristics

A total of 9270 patients with IS or TIA during the index period were identified, of whom 7978 (86.1%) received antiplatelet therapy and 1292 (13.9%) did not receive any antithrombotic treatment within 90 days of hospital discharge (Table 1). In the overall population, the mean age was 72.2 years and 47.3% of patients were female. The most common comorbidities in the overall study population were hypertension (47.7%), diabetes (16.9%), renal disease (16.5%), and chronic obstructive pulmonary disease (14.9%). A total of 479 (5.2%) patients included in the study had previously reported major bleeding. Among the untreated cohort, a slightly higher proportion of patients, about 6.5%, reported major bleeding while among the treated cohort 5.0% of the patients reported major bleeding at the baseline.

Treatment Patterns

A total of 7978 patients received antiplatelet therapy, of which clopidogrel SAPT (74.8%), aspirin SAPT (16.7%), and clopidogrel + aspirin DAPT (5.9%) were the most frequent (Table 2). Overall, few patients were treated with aspirin + dipyridamole ($n = 97$), dipyridamole

Table 1 Patient characteristics and comorbidities

	All patients (N = 9270)	Treated (n = 7978)	Untreated (n = 1292)	Clopidogrel SAPT (n = 5971)	Aspirin SAPT (n = 1332)	Clopidogrel + aspirin DAPT (n = 470)
Female, *n* (%)	4389 (47.3)	3723 (46.7)	666 (51.5)	2789 (46.7)	668 (50.2)	179 (38.1)
Age, years						
Mean	72.2 (13.8)	72.2 (13.3)	71.8 (16.1)	71.8 (13.4)	74.3 (13.2)	70.2 (13.3)
Distribution, *n* (%)						
18–54 years	1107 (11.9)	881 (11.0)	226 (17.5)	685 (11.5)	114 (8.6)	68 (14.5)
55–64 years	1438 (15.5)	1266 (15.9)	172 (13.3)	986 (16.5)	174 (13.1)	79 (16.8)
65–74 years	2195 (23.7)	1963 (24.6)	232 (18.0)	1494 (25.0)	296 (22.2)	120 (25.5)
75–79 years	1347 (14.5)	1176 (14.7)	171 (13.2)	847 (14.2)	211 (15.8)	73 (15.5)
≥ 80 years	3183 (34.3)	2692 (33.7)	491 (38.0)	1959 (32.8)	537 (40.3)	130 (27.7)
Comorbidities, *n* (%)						
Hypertension	4425 (47.7)	3870 (48.5)	555 (43.0)	2817 (47.2)	683 (51.3)	262 (55.7)
Diabetes	1571 (16.9)	1402 (17.6)	169 (13.1)	985 (16.5)	259 (19.4)	120 (25.5)
Renal disease	1529 (16.5)	1318 (16.5)	211 (16.3)	919 (15.4)	269 (20.2)	86 (18.3)
Chronic obstructive pulmonary disease	1377 (14.9)	1170 (14.7)	207 (16.0)	829 (13.9)	215 (16.1)	88 (18.7)
Cancer	817 (8.8)	663 (8.3)	154 (11.9)	500 (8.4)	105 (7.9)	35 (7.4)
MI	711 (7.7)	635 (8.0)	76 (5.9)	360 (6.0)	138 (10.4)	102 (21.7)
Peripheral vascular disease	553 (6.0)	470 (5.9)	83 (6.4)	325 (5.4)	84 (6.3)	44 (9.4)
Major bleeding	479 (5.2)	395 (5.0)	84 (6.5)	287 (4.8)	74 (5.6)	23 (4.9)
Heart failure	381 (4.1)	332 (4.2)	49 (3.8)	226 (3.8)	63 (4.7)	26 (5.5)

DAPT dual antiplatelet therapy, *MI* myocardial infarction, *SAPT* single antiplatelet therapy

(n = 44), ticagrelor (n = 3), or prasugrel (n = 1). Therefore, these treatment groups were not examined further due to the small sample size being prone to error and can potentially leading to imprecise outcomes.

Almost all patients (99.9%) in the clopidogrel SAPT cohort received the 75-mg dose, and only two patients received 300 mg. Among the aspirin SAPT cohort, 92% received the 75-mg dose and 8% received the 300-mg dose. The median duration of therapy was slightly lower among patients who received aspirin SAPT compared to those who received clopidogrel SAPT or DAPT (232 vs. 294 and 300 days, respectively), and the mean length of hospital stay ranged between 8.5 and 11.7 days in the treated cohort compared to 22.7 days in the untreated cohort. Of the patients initiating DAPT, 62.3% switched to SAPT (82.6% to clopidogrel and 17.4% to aspirin), with a median time to switch of 56 days. At 3 months after initial hospitalization, the probabilities of treatment discontinuation among patients treated with clopidogrel SAPT, aspirin SAPT,

Table 2 Treatment patterns in hospitalized adult patients with TIA or IS receiving antiplatelet therapy

	Clopidogrel SAPT (*n* = 5971)	Aspirin SAPT (*n* = 1332)	Clopidogrel + aspirin DAPT (*n* = 470)
Duration of treatment, days, median (25th, 75th percentile)	294 (107, 657)	232 (83, 588)	300 (126, 735)
Switched to SAPT, *n* (%)	–	–	293 (62.3)
Aspirin	–	–	51 (17.4)
Clopidogrel	–	–	242 (82.6)
Time to switch to SAPT, days, median (25th, 75th percentile)	–	–	56 (28, 100)
Length of hospital stay, days, mean (SD)[a]	10.9 (17.6)	11.7 (20.0)	8.5 (12.2)

DAPT dual antiplatelet therapy, *IS* ischemic stroke, *SAPT* single antiplatelet therapy, *SD* standard deviation, *TIA* transient ischemic attack

[a]The mean length of hospital stay in the untreated cohort was 22.7 days (SD, 32.1)

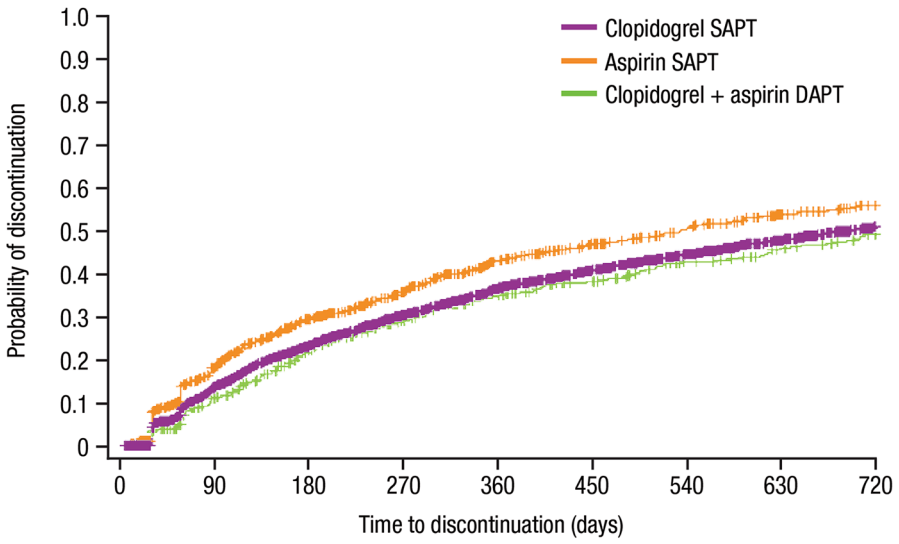
and clopidogrel + aspirin DAPT were 14.1, 18.6, and 11.4%, respectively. These discontinuation rates increased to 36.9, 43.4, and 35.1% at 1 year and to 51.2, 56.3, and 49.4% at 2 years, respectively (Fig. 2). The aspirin SAPT cohort had a relatively higher discontinuation rate compared to the clopidogrel SAPT cohort, which may be potentially attributed to differences in baseline characteristics (e.g., the aspirin cohort was relatively older with higher comorbidity burden).

Treatment Outcomes

Treatment outcomes were assessed in 7948 patients who initiated antiplatelet treatment with clopidogrel SAPT (*n* = 5969), aspirin SAPT (*n* = 1307), or clopidogrel + aspirin DAPT (*n* = 470) and 1292 untreated patients (30 patients were excluded from the outcomes analysis because they discontinued index antiplatelet therapy before their discharge date).

The rates of IS, MI, major bleeding, cardiovascular-related mortality, and all-cause mortality up to 3 years post-discharge according to antiplatelet therapy are shown in Table 3. At 1 year post-discharge, the incidence rates per 100 person-years for treated and untreated patients were as follows: IS, 6.5 and 14.9; major bleeding, 4.1 and 8.6; cardiovascular-related mortality, 5.0 and 28.2; and all-cause mortality, 7.3 and 39.8, respectively (Table 3). Similar results were observed at 3 years post-discharge. There were few MI events in both treated and untreated patients through 3 years post-discharge; 0.7 per 100 person-years for both groups at 1 year; 1.0 (untreated) and 0.6 (treated) at 3 years (Table 3). Within the individual treatment cohorts, the incidences of IS, MI, and major bleeding were generally similar in those who received aspirin SAPT, clopidogrel SAPT, and DAPT. The incidence of cardiovascular-related and all-cause mortality appeared higher among patients who received aspirin SAPT compared to those who received clopidogrel SAPT or DAPT, which may be driven in part by differences in patient characteristics between the groups.

Patients who received antiplatelet therapy also had numerically lower rates of MACE 1 (IS, MI, or cardiovascular-related mortality) and MACE 2 (overall stroke, MI, or all-cause mortality) outcomes than patients who did not receive treatment (Table 3), though the cause of this numerical difference could not be determined. The bleeding incidences were relatively low, as compared with other health outcomes.



Number of patients									
Clopidogrel SAPT	5971	4684	3756	3121	2583	2196	1872	1577	1325
Aspirin SAPT	1332	968	756	614	492	417	363	305	262
Clopidogrel + aspirin	470	379	306	253	214	186	155	138	121
Probability of discontinuation									
Clopidogrel SAPT	0	0.141	0.237	0.307	0.369	0.412	0.448	0.481	0.512
Aspirin SAPT	0	0.186	0.296	0.362	0.434	0.473	0.511	0.540	0.563
Clopidogrel + aspirin DAPT	0	0.114	0.224	0.293	0.351	0.386	0.431	0.462	0.494

Fig. 2 Probability of treatment discontinuation in patients receiving clopidogrel SAPT, aspirin SAPT, and clopidogrel + aspirin DAPT. The number of patients remaining on treatment and the probability of treatment discontinuation at each time point are presented below the chart. *DAPT* dual antiplatelet therapy, *SAPT* single antiplatelet therapy

DISCUSSION

In the United Kingdom, stroke is the third leading cause of years of life lost and of disability-adjusted life-years [21]. The associated costs are extremely high, and interventions aimed at reducing recurrent stroke are an important strategy in reducing the societal burden of this disease [5, 22]. This study contributes to the limited data available about the treatment patterns and associated clinical outcomes for SSP among patients in the United Kingdom. Clopidogrel was the most frequently used antiplatelet therapy, while aspirin use was associated with a shorter duration of treatment. Further, the probability of discontinuation within 2 years of treatment initiation was similar in patients receiving SAPT or DAPT. Of note, the high rates of discontinuation observed in this study are consistent with studies from different data sources and countries that also found suboptimal persistence rates of oral drugs used for preventative purposes, including antiplatelets [23–25]. Also, this study found that the clinical outcomes are numerically different between cohorts, but the results need to be interpreted with caution due to impact of confounding factors (e.g., observed and unobserved differences in characteristics and risk profile across cohorts, especially between treated and untreated cohorts). However, many factors contributing to the observed clinical differences are currently unknown due to limitations of study design and data sources, highlighting the need for future studies to confirm underlying reasons behind these variations.

There is clear clinical evidence supporting the use of antiplatelet therapy for SSP in patients with TIA or IS [26], with recent efforts aimed at reducing the risk of IS while also minimizing the risk of bleeding using DAPT. In

Table 3 Incidence rates (per 100 person-years) of IS, MI, major bleeding, cardiovascular-related mortality, all-cause mortality, MACE 1, and MACE 2, according to treatment pattern

	All patients (*N* = 9240)	**Antiplatelet treatments of interest (*n* = 7746)**	**Untreated (*n* = 1292)**	**Clopidogrel SAPT (*n* = 5969)**	**Aspirin SAPT (*n* = 1307)**	**Clopidogrel + aspirin DAPT (*n* = 470)**
IS, *n* (per 100 person-years)						
3 months	327 (16.0)	243 (13.5)	76 (39.6)	191 (13.7)	34 (11.4)	18 (16.6)
1 year	435 (7.3)	341 (6.5)	85 (14.9)	260 (6.3)	58 (6.9)	23 (7.1)
2 years	494 (5.6)	391 (5.1)	91 (10.2)	302 (5.0)	63 (5.3)	26 (5.4)
3 years	517 (5.1)	413 (4.7)	92 (8.5)	320 (4.6)	66 (4.8)	27 (4.7)
MI, *n* (per 100 person-years)						
3 months	16 (0.8)	11 (0.6)	3 (1.5)	5 (0.4)	4 (1.3)	2 (1.8)
1 year	46 (0.7)	39 (0.7)	4 (0.7)	25 (0.6)	10 (1.2)	4 (1.2)
2 years	62 (0.7)	50 (0.6)	9 (0.9)	32 (0.5)	11 (0.9)	7 (1.4)
3 years	71 (0.7)	57 (0.6)	11 (1.0)	37 (0.5)	12 (0.8)	8 (1.4)
Major bleeding, *n* (per 100 person-years)						
3 months	119 (5.7)	83 (4.5)	34 (17.0)	54 (3.8)	17 (5.7)	12 (10.8)
1 year	277 (4.5)	220 (4.1)	51 (8.6)	156 (3.7)	44 (5.2)	20 (6.0)
2 years	365 (4.1)	301 (3.9)	56 (6.1)	217 (3.6)	53 (4.4)	31 (6.3)
3 years	415 (4.0)	340 (3.8)	65 (5.8)	244 (3.5)	62 (4.4)	34 (5.9)
Cardiovascular-related mortality, *n* (per 100 person-years)						
3 months	265 (12.7)	123 (6.7)	138 (67.6)	77 (5.4)	38 (12.6)	8 (7.2)
1 year	451 (7.3)	271 (5.0)	172 (28.2)	178 (4.2)	77 (8.9)	16 (4.7)
2 years	561 (6.2)	360 (4.5)	191 (20.1)	245 (3.9)	97 (7.8)	18 (3.6)
3 years	616 (5.8)	404 (4.4)	201 (17.4)	278 (3.9)	105 (7.3)	21 (3.5)
All-cause mortality, *n* (per 100 person-years)						
3 months	352 (16.8)	167 (9.1)	180 (88.1)	102 (7.1)	53 (17.5)	12 (10.8)
1 year	650 (10.5)	396 (7.3)	243 (39.8)	265 (6.3)	108 (12.5)	23 (6.8)

Table 3 continued

	All patients (N = 9240)	Antiplatelet treatments of interest (n = 7746)	Untreated (n = 1292)	Clopidogrel SAPT (n = 5969)	Aspirin SAPT (n = 1307)	Clopidogrel + aspirin DAPT (n = 470)
2 years	810 (8.9)	524 (6.6)	272 (28.6)	364 (5.9)	134 (10.8)	26 (5.1)
3 years	891 (8.4)	588 (6.4)	288 (24.9)	412 (5.7)	146 (10.2)	30 (5.0)
MACE 1 outcomes, n (per 100 person-years)						
3 months	586 (28.8)	365 (20.3)	207 (108.3)	265 (19.0)	74 (25.0)	26 (24.0)
1 year	889 (14.9)	627 (11.9)	243 (43.0)	444 (10.8)	140 (16.8)	43 (13.3)
2 years	1063 (12.2)	769 (10.1)	271 (30.7)	552 (9.2)	166 (13.9)	51 (10.6)
3 years	1149 (11.3)	840 (9.5)	285 (26.6)	608 (8.8)	176 (12.8)	56 (9.9)
MACE 2 outcomes, n (per 100 person-years)						
3 months	670 (33.0)	409 (22.8)	247 (129.2)	290 (20.8)	89 (30.0)	30 (27.7)
1 year	1079 (18.1)	749 (14.2)	309 (54.7)	529 (12.9)	170 (20.4)	50 (15.4)
2 years	810 (8.8)	524 (6.8)	272 (21.1)	364 (6.1)	134 (10.3)	26 (5.5)
3 years	1404 (13.8)	1015 (11.5)	363 (33.8)	734 (10.6)	216 (15.7)	65 (11.5)

SAPT single antiplatelet therapy, *DAPT* dual antiplatelet therapy, *IS* ischemic stroke, *MI* myocardial infarction, *MACE* major adverse cardiac event
MACE 1 = IS, MI, or cardiovascular-related mortality
MACE 2 = overall stroke, MI, or all-cause mortality

particular, data from the Clopidogrel in High-risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) and POINT studies demonstrate clear reductions in recurrent IS with the combination of aspirin and clopidogrel compared to aspirin alone [15, 27]. In the CHANCE trial, the risk of recurrent stroke was reduced by 32% in patients receiving DAPT with clopidogrel + aspirin within 24 h after symptom onset compared to aspirin alone [27]. The rates of moderate-to-severe bleeding events were similar in both treatment arms. Similarly, in the POINT trial, there was a 25% reduction in the risk of major ischemic events (IS, MI, or death from an ischemic vascular event) at 90 days in patients receiving DAPT with clopidogrel + aspirin compared with aspirin alone [15]. However, in the POINT study, the use of DAPT was also associated with a significantly higher risk of major hemorrhage compared to aspirin alone, which occurred after being treated beyond 21 days [28]. Subsequently, a series of meta-analyses have confirmed a reduction in the absolute risk of recurrent stroke following the administration of DAPT within 24 h of IS or TIA. The benefit–risk ratio is optimized with

short duration therapy, while the risk of bleeding events is increased with longer duration therapy [29–31]. Based on these studies, stroke treatment guidelines now recommend SSP with clopidogrel + aspirin DAPT for 21 days in patients with TIA or minor stroke while also minimizing the risk of bleeding [12–14].

Based on long-term follow-up results from a large registry study of patients with TIA or minor stroke, the rate of cardiovascular events including stroke was 6.4% in the first year and 6.4% in the second through fifth years, showing sustained risk over a period of 5 years, which emphasized the need for preventing secondary stroke in the long run [32]. Because continued SSP is important in reducing the rate and severity of recurrent stroke, there is a need for new treatment strategies that are safe and effective for long-term SSP.

Strengths of the current study include the linked databases across CPRD, HES, and ONS, which provide the opportunity to examine a fuller picture of patient care compared with any one of the stand-alone databases. In detail, antiplatelet use can be captured within the CPRD claims among patients discharged from the hospital due to IS/TIA (HES data), and cardiovascular-related death can be obtained from ONS mortality data. Therefore, the antiplatelet treatment patterns, clinical outcomes, and mortality information were fully captured in this study, and linkages like this are not readily available in many other claims data sources. Also, the CPRD database is representative of the general UK population since the United Kingdom has universal health coverage and uses primary care as a gatekeeper that can monitor the effectiveness and safety of a treatment. The main limitations of this study are the potential underestimation of the treated, particularly those who use aspirin, arising from missing data or excluded patients. For example, prescriptions issued in secondary care are not recorded in CPRD, and diagnostic codes from secondary care may not be consistently coded within the database; patients with a diagnosis of AF were excluded from this study to ensure stroke as the primary cause of antiplatelet use, which therefore contributed to underestimation of SSP cases; the relatively higher cost of the National Health Service (NHS) prescription fee compared to the over-the-counter (OTC) cost of aspirin may prompt patients to opt for OTC purchases that consequently underestimates the actual use of aspirin. Also, future studies may explore factors associated with SSP, such as controlling for baseline, socioeconomic, and clinical characteristics between cohorts. Many of those characteristics (e.g., stroke severity as measured in National Institutes of Health Stroke Scale [NIHSS]) are not available in the data sources. Finally, the assessments of clinical outcomes were started after patient discharge, and any early IS events that occurred prior to discharge would not have been captured.

CONCLUSIONS

In conclusion, data from this large real-world database analysis indicate that many patients in the United Kingdom at risk of secondary stroke might not be receiving or had discontinued antiplatelet therapy despite recommendations of long-term SAPT [13]. In addition, for those receiving DAPT, the median time to switch to SAPT was 56 days, which was within the range of moderate recommendations of 90 days [33], but more than double the strong recommendation of up to 21 days [13]. This may indicate dissatisfaction with the treatment either to prevent IS/TIA or with the concern of bleeding risk. Improved therapies for long-term SSP are needed that may lead to higher treatment and persistence rates and, therefore, improved outcomes in this patient population.

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Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Xuejun Liu was an employee of Bristol Myers Squibb at the time of the study and is a current PhD candidate of the University of North Carolina at Chapel Hill, School of Public Health. Jenny Jiang, Danshi Li, Jay Horrow, Anja Kahl, and Xiaoyan Li are current employees of Bristol Myers Squibb. Hiroshi Tamada was an employee of Bristol Myers Squibb at the time of the study and is currently employed as the founder of Nassau Biopharma Consulting. Vignesh Hariharan was an employee of Mu Sigma Inc. at the time of the study and is a current employee of Accenture. Ankur Avinav was an employee of Mu Sigma Inc. at the time of the study and is a current employee of Indium Software.

Ethical Approval. This article had been approved by the Independent Scientific Advisory Committee (ISAC), with the reference number ISAC19_240R. Although this study does not involve primary data collection from human participants, it was performed in accordance with the ethical principles set forth in the Helsinki Declaration of 1964 and its later amendments. Given that this study was based on retrospective analyses of secondary databases without enrollment of patients, all data were anonymized and de-identified prior to analysis.

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