Antithrombotics prescription and adherence among stroke survivors: A systematic review and meta-analysis

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Abstract

Objectives: We aimed to investigate the prescription of antithrombotic drugs (including anticoagulants and antiplatelets) and medication adherence after stroke.

Methods: We performed a systematic literature search across MEDLINE and Embase, from January 1, 2015, to February 17, 2022, to identify studies reporting antithrombotic medications (anticoagulants and antiplatelets) post stroke. Two people independently identified reports to include, extracted data, and assessed the quality of included studies according to the Newcastle–Ottawa scale. Where possible, data were pooled using random-effects meta-analysis.

Results: We included 453,625 stroke patients from 46 studies. The pooled proportion of prescribed antiplatelets and anticoagulants among patients with atrial fibrillation (AF) was 62% (95% CI: 57%–68%), and 68% (95% CI: 58%–79%), respectively. The pooled proportion of patients who were treated according to the recommendation of guidelines of antithrombotic medications from four studies was 67% (95% CI: 41%–93%). It was reported that 11% (95% CI: 2%–19%) of patients did not receive antithrombotic medications. Good adherence to antiplatelet,
anticoagulant, and antithrombotic medications was 78% (95% CI: 67%–89%), 71% (95% CI: 57%–84%), and 73% (95% CI: 59%–86%), respectively.

**Conclusion:** In conclusion, we found that less than 70% of patients were prescribed and treated according to the recommended guidelines of antithrombotic medications, and good adherence to antithrombotic medications is only 73%. Prescription rate and good adherence to antithrombotic medications still need to be improved among stroke survivors.

**Keywords**
anticoagulant, antiplatelet, antithrombotic, secondary prevention, stroke, systematic review

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**1 | INTRODUCTION**

Recurrent strokes account for approximately 20% of all strokes (Benjamin et al., 2018). The cause of stroke recurrence includes nonadherence to antithrombotic treatment (Broderick et al., 2011). Antithrombotic agents (anticoagulants and antiplatelets) are among important factors to prevent short- and long-term recurrence of ischemic stroke (Del Brutto et al., 2019). Patients with stroke with high medication adherence have lower incidence of adverse outcomes compared to those with low medication adherence (Kim et al., 2017; Perreault et al., 2012; Rijkmans et al., 2018). Despite this, the secondary prevention measures after stroke have shown significant gaps in specialist care, monitoring, and treatment programs (Broderick et al., 2011; Webb et al., 2019; Weimar et al., 2013). The European Stroke Action Plan (ESAP) for the years 2018–2030 outlined targets for the development of stroke care, one of which is secondary prevention and organized follow-up (Norrving et al., 2018).

To summarize the prescription rate and patient medication adherence of antithrombotics after stroke, we conducted this systematic review and meta-analysis synthesizing the evidence on the optimal antithrombotic treatment and adherence according to guidelines for the secondary prevention of stroke.

**2 | MATERIALS AND METHODS**

The systematic review was reported following Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). We reviewed only previously published data, and ethics committee approval and all subjects informed consent were not required.

**2.1 | Search strategy**

A comprehensive search strategy (the Appendix), which was developed in consultation with a university librarian, neurologists, and epidemiologists, was used to address the unique features and indexing of each of the two electronic databases (Medline and Embase) that were searched from January 1, 2015, to February 17, 2022. As well as searching for original studies, the reference lists of any relevant reviews appearing in their reports were examined.

**2.2 | Selection criteria**

Any studies reporting antithrombotic medications (anticoagulants and antiplatelets) after stroke (ischemic or hemorrhagic) or transient ischemic attack (TIA) were included. Patients aged 18 years and over, of any race with a clinical or imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) diagnosis of stroke, were included. There were no language restrictions.

**2.3 | Data extraction and quality assessment**

MY and HC independently screened the titles and abstracts, excluded irrelevant references, and reviewed abstracts of potential relevance to identify reports for review in full text. MY and HC extracted data independently from the included studies. MO and SS assessed the quality of included studies according to the Newcastle–Ottawa scale (NOS) (Stang, 2010). Any disagreements were resolved by a third author (XW or JY).

**2.4 | Outcomes**

The main outcomes were the proportion of patients prescribed and using (adherence) antithrombotic medication after stroke. Medication adherence refers to the extent to which patients act in accordance with the prescribed interval and dose of the medication regimen. Medication persistence was defined as the duration of time from initiation to discontinuation of therapy (Cramer et al., 2008). Good adherence to the medications was defined by continuation of medications (Ullberg et al., 2017) or prescription refill, for example, Continuous Measure of Medication Acquisition (CMA) (Hess et al., 2006), the proportion of days covered (PDC) (Yeo et al., 2020), or the 4-item Morisky Medication Adherence Scale (MMAS-4) (Morisky et al., 1986).
| Author            | Country    | Study design                        | Subtype                           | Number of subjects | Age (mean, SD) | Sex (female, %) |
|-------------------|------------|-------------------------------------|-----------------------------------|--------------------|----------------|-----------------|
| Bergstrom 2017    | Sweden     | Population-based study/national registry | Ischemic stroke                  | 196765             | 76 (11.4)     | 50              |
| Mechtouff 2018     | France     | Single-center hospital-based study  | Ischemic stroke or tia            | 373                | <60 (24.9%)    | 43              |
| Faure 2020         | Canada     | Population-based study/national registry | Ischemic stroke                  | 5587               | <65 (17.3%)    | 50              |
| Jithin 2016        | India      | Single-center hospital-based study  | Ischemic stroke                  | 295                | <60 (42.0%)    | 39              |
| Eriksson 2017      | Sweden     | Single-center hospital-based study  | Stroke                           | 549                | 70             | 48              |
| Rijkmans 2018      | The Netherland | Single-center hospital-based study  | Ischemic stroke                  | 286                | 70             | 48              |
| Desmaele 2016      | International | Multi-center hospital-based study | Stroke                           | 247                | 68.6 (60.0-75.4) | 47              |
| Zhang 2017         | China      | Multi-center hospital-based study   | Ischemic stroke & AF             | 1014               | 70.3 (10.8)    | 54              |
| Lim 2015           | Korea      | Multi-center hospital-based study   | Tia                              | 500                | 64.4 (11.8)    | 42              |
| Park 2017          | Korea      | Multi-center hospital-based study   | Ischemic stroke or tia            | 9506               | 65.9 (12.7)    | 39              |
| Ullberg 2017       | Sweden     | Population-based study/national registry | Ischemic stroke                  | 5602               | 73             | 47              |
| Sarfo 2016         | Ghana      | Single-center hospital-based study  | Stroke                           | 418                | 60             | 50              |
| Sluggett 2015      | Australia  | Population-based study/national registry | Ischemic stroke or tia         | 1541               | 85             | 51              |
| Jiang 2017         | China      | Population-based study/national registry | Ischemic stroke or tia         | 18344              | 64 (56-73)     | 36              |
| Brewer 2015        | United Kingdom | Multi-center hospital-based study | Ischemic stroke                  | 302                | >= 65 (66%)    | 43              |
| Haeusler 2015      | Germany    | Population-based study/national registry | Ischemic stroke or tia & AF         | 896                | 71.3 (9.6)     | 43              |
| Yeo 2020           | Singapore  | Population-based study/national registry | Ischemic stroke                  | 1215               | 65.3 (13.4)    | 38              |
| Mazurek 2017       | United Kingdom | Population-based study/national registry | Stroke & AF                     | 428                | 79.6 (9.6)     | 45              |
| Abdo 2019          | Lebanon    | Multi-center hospital-based study   | Ischemic stroke or TIA           | 173                | 69.8 (12.7)    | 40              |
| Magwood 2017       | United States | Population-based study/national registry | Stroke                        | 125                | 39.6 (7.7)     | 54              |
| Akijian 2017       | United Kingdom | Population-based study/national registry | TIA                           | 172                | 71 (12.2)      | 51              |
| Akijian 2017       | United Kingdom | Population-based study/national registry | Ischemic stroke                  | 412                | 71.4 (13.4)    | 49              |
| Sauer 2015         | Germany    | Single-center hospital-based study  | Ischemic stroke & AF             | 284                | 78.1 (9.5)     | 51              |
| Xian 2015          | United States | Population-based study/national registry | Ischemic stroke & AF           | 12552              | 80.5 (7.6)     | 60              |
| Shah 2016          | Canada     | Multi-center hospital-based study   | Ischemic stroke or TIA & AF      | 5781               | –              | 46              |

(Continues)
| Author               | Country          | Study design                             | Subtype                           | Number of subjects | Age (mean, SD) | Sex (female, %) |
|----------------------|------------------|------------------------------------------|-----------------------------------|--------------------|----------------|-----------------|
| Guidoux 2019 (Guidoux et al., 2019) | France           | Multi-center hospital-based study         | Stroke & AF                       | 400                | 78.7 (11.0)    | 52              |
| Xu 2017 (Xu et al., 2016)      | China            | Single-center hospital-based study        | Ischemic stroke                   | 878                | 63.2 (13.1)    | 35              |
| Jurjans 2019 (Jurjans et al., 2019) | Latvia           | Single-center hospital-based study        | Ischemic stroke & AF              | 682                | 80 (75-85)     | 69              |
| Saade 2021 (Saade et al., 2021) | Lebanon          | Multi-center hospital-based study         | Ischemic stroke                   | 100                | 74.0 (10)      | 43              |
| Gynnild 2021 (Gynnild et al., 2021) | Norway           | Multi-center hospital-based study         | Ischemic stroke                   | 664                | 72.9 (11.5)    | 43              |
| Dalli 2020 (Dalli et al., 2021) | Australia        | Population-based study/national registry  | Stroke or TIA                     | 9817               | 74.2 (63.3, 82.5) | 45              |
| Yeo 2020 (Yeo et al., 2020)     | Singapore        | Population-based study/national registry  | Ischemic stroke                   | 3469               | -              | 44              |
| Shankari 2020 (Shankari et al., 2020) | Singapore      | Single-center hospital-based study        | Ischemic stroke or TIA            | 199                | 62.9 (11.9)    | 36              |
| Malaeb 2020 (Malaeb et al., 2020) | Lebanon          | Multi-center hospital-based study         | Ischemic stroke                   | 204                | 65.4 (11.9)    | 33.3            |
| MacDonald 2020 (MacDonald et al., 2020) | United States    | Multi-center hospital-based study         | Stroke                            | 107                | 56.0 (11.2)    | 42.1            |
| Gronemann 2020 (Gronemann et al., 2020) | Germany         | Population-based study/national registry  | Ischemic stroke & AF              | 1512               | 76.7 (9.6)     | 53.3            |
| Flach 2020 (Flach et al., 2020)  | United Kingdom  | Population-based study/national registry  | Stroke                            | 6052               | <65 (34%)      | 49              |
| Chang 2020 (Chang et al., 2020) | United States   | Population-based study/national registry  | Stroke & AF                       | 64228              | 84 (78-89)     | 63              |
| Abanto 2020 (Abanto et al., 2020) | Peru             | Population-based study/national registry  | Stroke                            | 150                | 66.3 (12.6)    | 38              |
| Chen 2019 (Chen et al., 2019)    | Canada           | Multi-center hospital-based study         | Ischemic stroke or TIA            | 408                | 68 (13)        | 47.5            |
| Chen 2019                     | Canada           | Multi-center hospital-based study         | Ischemic stroke or TIA            | 392                | 70 (11)        | 43.1            |
| Dalli 2021 (Dalli et al., 2021) | Australia        | Multi-center hospital-based study         | Stroke or TIA                     | 8363               | ≥75 (44%)      | 44              |
| Kim 2021 (Kim et al., 2021)     | South Korea      | Population-based study/national registry  | Ischemic stroke                   | 4621               | 66.4 (12.3)    | 43.8            |
| Kothagundla 2021 (Kothagundla et al., 2021) | India          | Single-center hospital-based study        | Stroke                            | 150                | 60 (1)         | 37              |
| Preinreich 2021 (Preinreich et al., 2021) | Austria     | Population-based study/national registry  | Stroke                            | 76354              | -              | -               |
| Rodríguez-Bernal 2021 (Rodríguez-Bernal et al., 2021) | Spain          | Population-based study/national registry  | Ischemic stroke or TIA & AF       | 10986              | 78.8 (9.3)     | 53.3            |
| Sheehan 2021 (Sheehan et al., 2021) | United States   | Population-based study/national registry  | Ischemic stroke                   | 172                | 75.0 (7.3)     | -               |
| Tiili 2021 (Tiili et al., 2021)  | Finland          | Population-based study/national registry  | Ischemic stroke & AF              | 396                | 75.0 (70–80)   | 43              |

AF: atrial fibrillation; IS: ischemic stroke; TIA: transient ischemic stroke.
TABLE 2  Quality assessment for the included studies

| Study              | Study type | Selection_1 | Selection_2 | Selection_3 | Selection_4 | Comparability | Outcome_1 | Outcome_2 | Outcome_3 | Total scale |
|--------------------|------------|-------------|-------------|-------------|-------------|---------------|------------|------------|------------|-------------|
| Abdo, 2019         | Cohort     | 1           | 1           | 0           | 1           | 0             | 0          | 0          | 1          | 4           |
| Akijian, 2017      | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 0          | 1          | 8           |
| Bergstrom, 2017    | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Brewer, 2015       | Cohort     | 1           | 1           | 1           | 1           | 0             | 1          | 1          | 0          | 6           |
| Chen, 2019         | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 0          | 8           |
| Dalli, 2021        | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 0          | 8           |
| Desmaele, 2016     | Cohort     | 1           | 1           | 1           | 1           | 0             | 0          | 1          | 0          | 5           |
| Eriksson, 2017     | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Kim, 2021          | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Faure, 2020        | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 8           |
| Jiang, 2017        | Cohort     | 1           | 1           | 1           | 1           | 1             | 0          | 1          | 0          | NA 5        |
| Jithin, 2016       | cross-sectional | 1   | 1            | 1            | 1            | 2             | 0          | 1          | 0          | 7           |
| Jurjans, 2019      | Cohort     | 0           | 1           | 1           | 1           | 0             | 0          | 1          | 1          | 5           |
| Lim, 2015          | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Magwood, 2017      | Cross-sectional | 1 | 0             | 0            | 0             | 1             | 1          | 1          | NA 4       |
| Kothagundla, 2021  | Cohort     | 1           | 1           | 1           | 1           | 1             | 0          | 1          | 0          | 7           |
| Mechtouff, 2018    | Cross-sectional | 1 | 0             | 0            | 2             | 2             | 1          | 1          | NA 7       |
| Park, 2017         | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 8           |
| Rijkmans, 2018     | Cohort     | 0           | 1           | 1           | 1           | 1             | 1          | 1          | 1          | 7           |
| Sarfo, 2016        | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 0          | 7           |
| Sluggett, 2015     | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 8           |
| Ullberg, 2017      | Cohort     | 1           | 1           | 1           | 1           | 1             | 0          | 1          | 0          | 6           |
| Yeo, 2020          | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Preinreich, 2021   | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 0          | 8           |
| Rodriguez-Bernal, 2021 | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 0          | 8           |
| Sheehan, 2021      | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 0          | 8           |
| Tiili, 2021        | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Guidoux, 2019      | Cohort     | 0           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 7           |
| Haeusler, 2015     | Cross-sectional | 1 | 0             | 1            | 0             | 2             | 1          | 1          | NA 6       |
| Mazurek, 2017      | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 8           |
| Sauer, 2015        | Cohort     | 0           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 7           |
| Shah, 2016         | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Xian, 2015         | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 8           |
| Xu, 2017           | Cohort     | 0           | 1           | 1           | 1           | 2             | 1          | 1          | 0          | 7           |
| Abanto, 2020       | Cross-sectional | 1 | 0             | 0            | 2             | 2             | 2          | 1          | NA 8       |
| Chang, 2020        | Cohort     | 1           | 1           | 1           | 1           | 2             | 1          | 1          | 1          | 9           |
| Dalli, 2020        | Cohort     | 1           | 1           | 1           | 1           | 2             | 0          | 1          | 1          | 8           |
TABLE 2 (Continued)

| Study          | Study type     | Selection_1 | Selection_2 | Selection_3 | Selection_4 | Comparability | Outcome_1 | Outcome_2 | Outcome_3 | Total scale |
|----------------|----------------|-------------|-------------|-------------|-------------|---------------|------------|------------|------------|-------------|
| Zhang, 2017    | Cross-sectional| 1           | 1           | 0           | 2           | 2             | 2          | 1          | NA         | 9           |
| Flach, 2020    | Cohort         | 1           | 1           | 1           | 2           | 1             | 1          | 1          | 1          | 9           |
| Gronemann, 2020| Cohort         | 1           | 1           | 1           | 2           | 1             | 1          | 1          | 1          | 9           |
| Gynnild, 2020  | Cohort         | 1           | 1           | 1           | 2           | 1             | 1          | 1          | 1          | 9           |
| MacDonald, 2020 | Cross-sectional| 1           | 0           | 0           | 1           | 1             | 2          | 1          | NA         | 6           |
| Malaeb, 2020   | Cross-sectional| 1           | 0           | 0           | 1           | 0             | 2          | 1          | NA         | 5           |
| Saade, 2021    | Cross-sectional| 1           | 0           | 0           | 2           | 0             | 1          | 1          | NA         | 5           |
| Shankari, 2020 | Cross-sectional| 1           | 0           | 0           | 2           | 2             | 1          | 1          | NA         | 7           |
| Yeo, 2020      | Cross-sectional| 1           | 0           | 1           | 2           | 2             | 2          | 1          | NA         | 9           |

2.5 Statistical analysis

The data were pooled using random-effects models where data were available. An $I^2$ statistic was considered to reflect low likelihood (0%–25%), moderate likelihood (26%–75%), and high likelihood (76%–100%) of differences beyond chance, as was a $P$ value of less than or equal to 0.05 for heterogeneity (Rothman et al., 2008). Statistical analysis was performed with Stata, version 16.

3 RESULTS

Of 54,407 references identified through the databases, 109 remained after screening titles and abstracts for relevance (Figure S1). Forty-six studies (453,625 patients) that satisfied the eligibility criteria were included in the review (Table 1). Of the 46 studies, 31 studies reported prescription of antiplatelets, and 11 reported anticoagulation among patients with atrial fibrillation (AF). Two studies were defined as low quality (scores < 5) on the NOS (Table 2).

3.1 Antiplatelet medications

3.1.1 Prescription rate of antiplatelet medications

The pooled proportion of prescribed antiplatelet medication is 62% (95% CI: 57%–68%) (Figure 1), with 62% (95% CI: 54%–70%), 71% (95% CI: 58%–85%), 55% (95% CI: 37%–72%), and 70% (95% CI: 55%–85%) at discharge, 1–6 months, 1–4 years, and 5 years post index stroke, respectively (Figure 1).

3.1.2 Medication adherence

Definitions for adherence are heterogeneous between studies (Table 3). Good adherence to antiplatelet is 78% (95% CI: 67%–89%) (Figure 2). The adherence rate is 79% (95% CI: 64%–95%), 72% (95% CI: 39%–106%), and 82% (95% CI: 80%–84%) for ≤1, 1–4, and ≥5 years post index stroke, respectively (Figure S2). Adherence reported by high-income countries (HICs) (77%, 95% CI: 63%–91%) was lower than that in the low-and-middle-income countries (LMICs) (81%, 95% CI: 64%–98%) (Figure S2).

3.2 Anticoagulant medications

3.2.1 Prescription rate of anticoagulant medications

The pooled proportion of prescribed anticoagulants among patients with AF is 68% (95% CI: 58%–79%) (Figure 3), with 62% (95% CI: 45%–78%), 77% (95% CI: 69%–85%), 78% (95% CI: 51%–105%), and 76% (95% CI: 73%–79%) at discharge, 1–6 months, 1–2 years, and 5 years post index stroke, respectively (Figure 3).

3.2.2 Medication adherence

Good adherence to anticoagulant is 71% (95% CI: 57%–84%) (Figure 2). The adherence rate is 76% (95% CI: 51%–102%), 64% (95% CI: 61%–67%), and 73% (95% CI: 33%–113%) for ≤1, 1–4, and ≥5 years post index stroke, respectively (Figure S3). Adherence reported
**FIGURE 1** Forest plot of prescribed antiplatelet medications
| Study           | Population | Time post index stroke | Definition                                                                 | Findings                                                                                                                                                                                                 |
|-----------------|------------|------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mechtouff, 2018 | IS or TIA  | 3 years and 6 years post index stroke | Continuous Measure of Medication Acquisition (CMA) was defined as medication adherence. CMA ≥ 80% | Adherence to any antithrombotic drugs was 82% and 72%, at 3 years and 6 years, respectively. Adherence to anticoagulant was 60% and 52%, at 3 years and 6 years, respectively. Adherence to the antiplatelet drug was 91% and 84%, at 3 years and 6 years, respectively. |
| Xu, 2017        | IS         | 5 years                | Discontinuation of antiplatelet therapy                                     | 165 Discontinued during follow up                                                                                                                                                                         |
| Yeo, 2020       | IS         | Unknown                | Adherence was defined using PDC: high (≥ 75%), intermediate (50%—74%), low (25%—49%), and very low (< 25%). | 29%, 18%, 20%, and 34% had high, intermediate, low, and very low adherence to antithrombotic medications, respectively.                                                                                   |
| Ullberg, 2017   | IS         | 4 months               | Primary drug adherence was defined as filling the first drug prescription within 120 days after stroke. | Drug adherence rates 4 months post-stroke were 96% for antiplatelet drugs, and 90% for warfarin.                                                                                                          |
| Ullberg, 2017   | IS         | 14 months              | Drug persistence at 14 months was defined as filling a prescription between 10 and 14 months after stroke. | Drug adherence rates 14 months post-stroke were 85% for antiplatelet drugs, and 69% for warfarin.                                                                                                          |
| Sarfo, 2016     | Stroke     | 1 year                 | Persistence was defined as the continuation of medications.                | Persistent rate was 95% for antiplatelets, and 50% for anticoagulants.                                                                                                                                   |
| Jiang, 2017     | IS or TIA  | 3 months               | Three-month persistence was defined as continuation of all secondary preventive medications prescribed at discharge. | Persistence at 3 months after discharge was 66.35% for antiplatelets, and 63.16% for warfarin.                                                                                                          |
| Mazurek, 2017   | Stroke & AF| 1 year                 | Persistence was defined as the continuation of medications.                | 56% were adherent to antithrombotic treatment                                                                                                                                                           |
| Gynnild, 2021   | Ischemic stroke | 3 months  | MMAS-4 = 4 (high adherence)                                               | 469/474 (99%)                                                                                                                                                                                          |
| Gynnild, 2021   | Ischemic stroke | 18 months | MMAS-4 = 4 (high adherence)                                               | 464/474 (98%)                                                                                                                                                                                          |
| Dalli, 2020     | stroke or TIA | 1 year             | Discontinuation was assessed among medication users and defined as having no medication supply for ≥ 90 days in the year postdischarge. | 2426/7112 (34.1)                                                                                                                                                                                        |
| Dalli, 2021     | stroke or TIA | 1 year             | Adherence to each medication group was estimated using the proportion of days covered (PDC) method from hospital discharge until the 1-year landmark date. | 3218/4845 (66.4)                                                                                                                                                                                        |
| Malaeb, 2020    | IS         | Post discharge         | Post discharge prescription medications.                                   | 149/204 (73%)                                                                                                                                                                                          |
| Kim, 2021       | IS         | 6 months               | Discontinuation was defined as when the antiplatelet agents were discontinued without refills throughout the rest of the observation period. | Prevalence of premature discontinuation of antiplatelets within 6 months was 25.3%                                                                                                                      |

(Continues)
TABLE 3  (Continued)

| Study         | Population | Time post index stroke | Definition                                                                 | Findings                                                                 |
|---------------|------------|------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Kim, 2021 IS  |            | 12 months              | Discontinuation was defined as when the antiplatelet agents were           | Prevalence of premature disconinuation of antiplatelets within 12 months was 35.5% |
|               |            |                        | discontinued without refills throughout the rest of the observation period. |                                                                          |
| Kim, 2021 IS  |            | 24 months              | Discontinuation was defined as when the antiplatelet agents were           | Prevalence of premature disconinuation of antiplatelets within 24 months was 58.5% |
|               |            |                        | discontinued without refills throughout the rest of the observation period. |                                                                          |
| Rijkmans, 2018| IS         | 5.5 years              | Discontinuation of medication was considered nonpersistent.               | Persistent rate was 90% for aspirin, 72% for dipyridamole, and 53% for anticoagulants. |
| Sheehan, 2021 | IS         | 10 months              | Medication persistence was defined as the continuation of medication      | Persistent rate was 87% for antithrombotics                               |
|               |            |                        | classes prescribed at hospital discharge.                                |                                                                          |

AF: atrial fibrillation; IS: ischemic stroke; TIA: transient ischemic stroke.

by HICs (73%, 95% CI: 57%–88%) was higher than that in the LMICs (63%, 95% CI: 57%–74%) (Figure S3).

3.3  | Adherence to antithrombotic medications

Good adherence to antithrombotic medications is 73% (95% CI: 59%–86%) (Figure 2). Studies that defined adherence using prescription refill had higher adherence rate of 74% (95% CI: 55%–93%) than studies that used medication continuation: 70% (95% CI: 60%–81%) (Figure S4). The adherence rate is 75% (95% CI: 57%–93%), 90% (95% CI: 74%–106%), and 72% (95% CI: 64%–79%) for ≤1, 1–4, and ≥5 years post index stroke, respectively (Figure S4). Adherence reported by HICs (73%, 95% CI: 58%–87%) was approximate to that in the LMICs (73%, 95% CI: 67%–79%) (Figure S4).

3.4  | Optimal treatment

The recommendations from major guidelines are summarized in table S1 (Coutts et al., 2014; Kleindorfer et al., 2021; Klijn et al., 2019; Liu et al., 2020; Ringleb et al., 2008). The proportion of patients who were treated according to the recommendation of guidelines of antithrombotic medications is 67% (95% CI: 41%–93%) (Figure 4). 11% (95% CI: 2%–19%) of patients did not receive any antithrombotic medications as recommended (Figure 5). Faure et al. (2020) reported that 36% of patients received ≥2 antiplatelets or a combination of antiplatelet and anticoagulant. Such combinations are not recommended because of the potential increased risk of bleeding (Table S1).

4  | DISCUSSION

In this systematic review and meta-analysis, we summarized the proportions of antithrombotic medication prescription and adherence in patients with stroke. We found that less than 70% of patients were prescribed and treated according to the recommended guidelines of antithrombotic medications. Good adherence to antiplatelet, anticoagulant, and antithrombotic medications was 78% (95% CI: 67%–89%), 71% (95% CI: 57%–84%), and 73% (95% CI: 59%–86%), respectively. It was reported that 11% (95% CI: 2%–19%) of patients did not receive antithrombotic medications.

We found the lowest rates of anticoagulant prescription in Asia, compared with Europe and Americas (Figure S5), which is in line with a previous study (Koziel et al., 2021). Moreover, our results show that prescription for antiplatelet medication is highest in Asia (Figure S6). This may be because large artery atherosclerosis was the leading ischemic stroke etiology in Asians and less anticoagulants were prescribed for Asian stroke patients with AF (Ornello et al., 2018).

In our results, the prescribing rate (68%) of anticoagulants for patients with AF has increased, compared to 45% in the past decade (Hsu et al., 2016). There are around only 50% of patients still taking anticoagulants therapy by 2 years in the past 5–10 years studies (Collings et al., 2017; Deitelzweig et al., 2013; Wang et al., 2016), whereas our statistical analysis showed that the good adherence rate is 64% for 1–4 years post index stroke. This may be due to promotion of the AF management guidelines, along with the improvement of educational and economic standards.

Although our prescription rate has increased from the previous decade, it is still less than 70%. We suspect that the insufficient
prescription rate may still exist for the following reasons: uncertainty about clinical benefits and risks, knowledge and experience deficit, competing medical issues, and medication cost (Gross et al., 2003; Kirley et al., 2016). There may be potential ways to increase antithrombotic drug prescription rates, for example, increasing physicians’ awareness of under-treatment, emphasizing accurate assessment of bleeding risk (Hsu et al., 2016), and addressing drug high cost in some areas.

We also found lower adherence rate with anticoagulant in low- and middle-income countries compared with that in high-income countries, which may be related to different educational levels and cultural concepts. We found lower adherence rate with antiplatelet drugs in high-income countries compared with that in low- and middle-income countries. This may be due to the fact that Asians are more afraid of the risk of bleeding from anticoagulants, so they prefer antiplatelet drugs, while patients in developed countries are the opposite (Lowres et al., 2019). Given the association of nonadherence with increased morbidity and mortality (Viswanathan et al., 2012), adequate measures taken to improve medication adherence should receive much more attention in stroke patients. These strategies can be: (1) medical insurance or medication cost was associated with medication adherence (Kronish et al., 2013; Wang et al., 2006) as reducing drug costs or increasing health insurance coverage may increase medication adherence; 2) large-scale, national public health campaigns to focus on groups of medications effective for secondary prevention in stroke may make patients or caregivers take notice; and 3) patient education regarding medications to improve adherence. Then regular follow-up visits and direct asking about medication adherence could be efficient.

There are several limitations in this meta-analysis. First, there is no common gold standard method for evaluating medication adherence, which may introduce measurement bias in our results. Second, the pooling data were highly heterogeneous; this was not explained by differences in patient characteristics. We conducted subgroup analyses to pool the same definitions, study design, country, and timepoint; however, residual heterogeneity persisted.
**FIGURE 3**  Forest plot of prescribed anticoagulants among patients with AF

**FIGURE 4**  Forest plot of guideline antithrombotics

**FIGURE 5**  Forest plot of not receive any antithrombotic medications as recommended
CONCLUSION

In conclusion, we found that less than 70% of patients were prescribed and treated according to the recommended guidelines of antithrombotic medications, and good adherence to antithrombotic medications is only 73%. Prescription rate and good adherence to antithrombotic medications still need to be improved among stroke survivors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/brb3.2752

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