# Managed Care Considerations

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**Abstract**

Stroke is the third leading cause of death in the United States and among the most costly diseases. Most strokes are categorized as ischemic, and 10% to 15% are preceded by a transient ischemic attack (TIA). Stroke survivors suffer levels of disability and handicap that range from mild to very severe, and they rarely make a complete recovery. Initial stroke patients are at considerable risk for recurrent stroke, which can compound a patient's impairment and associated costs.

This article discusses the burden of stroke on patients and caregivers, the risk of stroke recurrence, and the pharmacoeconomics of antiplatelet therapy. Studies show that effective secondary prevention such as antiplatelet therapy can improve clinical outcomes in patients who have experienced TIA or prior stroke. Recently updated guidelines for secondary stroke prevention from the American Heart Association/American Stroke Association recommend administering antiplatelet agents rather than anticoagulants for patients who experienced an ischemic noncardioembolic stroke or TIA to reduce the risk of stroke or other cardiovascular events. The guidelines state that aspirin (ASA), ASA + extended-release dipyridamole (DP), and clopidogrel are acceptable initial treatment options for these patients.

A recent pharmacoeconomic analysis of all 3 therapies concluded that ASA and ASA + DP offer cost-effective secondary prevention for patients who have suffered a mild initial stroke. Understanding the role of antiplatelet therapy in secondary prevention can help the managed care community optimize clinical and economic outcomes, thereby reducing the overall burden of cerebrovascular disease.

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For author information and disclosures, see end of text.

In the past decade, the managed care community has focused heavily on reducing cardiometabolic risk factors such as hypertension, dyslipidemia, diabetes, and smoking. Quality initiatives for cardiovascular risk reduction include pay-for-performance programs[1] and improving performance using the Healthcare Effectiveness Data and Information Set (HEDIS) measures developed by the National Committee for Quality Assurance.[2] Stroke prevention has been subsumed within the broader context of cardiovascular disease (CVD); however, evidence suggests that considerations unique to secondary stroke prevention—particularly antiplatelet therapy—afford managed care the opportunity to optimize clinical and economic outcomes. This article discusses the burden of stroke, the risk of stroke recurrence, and the pharmacoeconomics of antiplatelet therapy.

## The Burden of Stroke

### *Epidemiology*

Each year in the United States, ~780,000 strokes occur, of which 180,000 are recurrent strokes.[3] Based on 2005 US population survey data, stroke prevalence among persons aged ≥18 years is an estimated 2.6% (2.7% for men and 2.5% for women). Prevalence increases with age. It also varies by ethnicity; stroke is more prevalent in Native Americans and blacks than in Hispanics, non-Hispanic whites, and Asians.[4]

Nearly 87% of strokes are ischemic, and the remaining 13% are hemorrhagic.[3] An analysis of data for 5017 patients included in a German stroke registry found that 25.6% of ischemic strokes were cardioembolic. Large artery disease accounted for 20.9% of noncardioembolic ischemic strokes, small vessel disease accounted for 20.5%, a total of 3.5% had other known causes, 6.9% could be attributed to more than one cause, and 22.7% were of undetermined origin.[5]

### *Impact of Stroke on the Patient*

*Mortality.* Stroke ranks third among all causes of death, after heart disease and cancer.[3] The mortality rate for patients who experience a recurrent stroke is higher than the mortality rate after an initial stroke. A study of Medicare patients noted a significantly higher 2-year survival rate following a first stroke (56.7%) as opposed to a recurrent stroke (48.3%). The disparity between survival rates

became evident within 1 to 3 months poststroke and increased over time.[6]

*Disability and Handicap.* The major sequelae of stroke for survivors are disability (loss of ability to carry out activities in the usual manner) and handicap (loss of ability to fulfill one's usual social roles), but stroke can impair virtually any human function. This includes gross and fine motor abilities, basic and instrumental activities of daily life, ambulation, language, perception, cognition, and mood.[7]

The levels of poststroke disability and handicap change over time, partly owing to the natural course of the disease, but also in relation to a patient's access to rehabilitation[7] and social support. Data from longitudinal and cross-sectional studies suggest that poststroke improvement is most rapid in the first month and plateaus by 3 months.[7] Despite this initial period of improvement, disability and handicap remain highly prevalent 1 and 3 years poststroke.[7,8] The pattern of recovery following a recurrent stroke is similar, but this is superimposed on any residual disability from the prior stroke. In a prospective observational study of 345 patients who suffered a disabling recurrent ischemic stroke, the rate of recovery was greatest during the first 6 months. Those patients who were not disabled prior to stroke recurrence and those whose disability was less severe after recurrence were most likely to recover functional independence. Patients left with moderate disability after stroke recurrence had a median recovery time of 6 months and those with severe disability required 18 months. Only 6% of patients left with very severe disability recovered by 18 months poststroke.[9]

*Stroke and Overall Health.* Comorbidities commonly associated with stroke include coronary heart disease (CHD) and peripheral arterial disease (PAD), which share some of stroke's risk factors. Direct sequelae of stroke include seizures,[10,11] complications related to immobility (eg, pressure sores, deep vein thrombosis, and pulmonary embolism), infections (eg, urinary tract and chest infections), pain,[10,11] aspiration,[12] and psychological dysfunction (especially depression).[11,13] As a result of chronic inactivity, stroke survivors sometimes develop long-term sequelae. Poor cardiorespiratory fitness increases a patient's risk for CVD and recurrent stroke.[14] Bone loss beyond that which is associated with normal aging has been observed in stroke patients and could lead to the development of osteoporosis.[15]

*Quality of Life (QOL).* A large US population survey found that stroke patients report significantly poorer QOL than individuals who have not suffered strokes.[16] A patient's levels of functional status and disability following a stroke are said to be important predictors of QOL.[17-19] Although higher functional status generally is associated with better QOL, patients with similar levels of disability might have very different perceptions about their QOL.[20] Poststroke depression is consistently tied to diminished QOL.[17,18,21-23] Other poststroke factors thought to correlate with QOL include fatigue,[22] cognitive impairment,[17] handicap or decreased participation,[24-26] social support,[19] and comorbidities.[27]

### *Impact of Stroke on the Caregiver*

Most stroke survivors live in the community, and most of their care is provided by family members, primarily spouses.[28] Because the onset of stroke is sudden, caregivers often have little time to adjust to their new role; this abrupt role change can disturb family relationships.[29] Even a mild stroke that produces minimal disability can have a major effect on QOL, psychological health, and family functioning for both patient and caregiver.[24] Caregivers of stroke patients commonly experience stress, sleep disturbance, anxiety, and depression. Their physical well-being may also be affected. Clinical symptoms and increased use of healthcare resources have been reported.[29] The impact of possible financial strain is another concern; the stroke patient may be unable to work due to functional disability, and the caregiver may stop working to provide care.[29]

### *The Cost of Stroke*

Stroke is one of the most expensive diseases in the United States. For noninstitutionalized US adults in 1997, cerebrovascular disease constituted the eighth most costly condition (after heart disease, cancer, trauma, mental disorders, pulmonary disease, diabetes, and hypertension) in terms of total annual direct expenditures. It was the most costly condition in terms of mean annual expendi-

ture per patient.[30] In 1991, the estimated mean lifetime cost (including direct and indirect costs) for a patient who suffered an ischemic stroke was $90,981,[31] which translates to $140,048 in 1999 dollars.[3] In 2008, the estimated annual direct and indirect costs of stroke in the United States totaled $65.5 billion.[3] Another study projected that the total direct and indirect costs of stroke from 2005 to 2050 would exceed $2.2 trillion (2005 dollars).[32]

Hospital care spending contributes significantly to the direct cost of stroke. The number of inpatients discharged from short-stay hospitals who received a primary diagnosis of stroke increased 20% from 1979 to 2005.[3] According to Nationwide Inpatient Survey data, hospital admissions for cerebrovascular diseases rose 12.8% in the decade between 1990-1991 and 2000-2001.[33] Although the mean length of the patient's hospital stay declined in this time period (eg, from 9.5 to 5.3 days for ischemic stroke), mean hospital charges per patient greatly increased (eg, jumping from $10,500 up to $16,200 for ischemic stroke). In-hospital stroke mortality rates decreased (eg, relative risk reduction was 36% for ischemic stroke), but the incremental cost for each survivor was $204,964.[33]

One study determined that the greatest cost drivers for incident stroke are acute hospitalization and inpatient rehabilitation, totaling $12,423 and $25,968 annually per person, respectively; the greatest cost drivers for prevalent stroke are nursing home care and lost earnings, at $33,636 and $22,880 annually per person, respectively. These estimates (in 2005 dollars) exclude strokes in people under 45 years of age and do not consider caregivers' lost earnings.[32]

Costs for recurrent stroke versus first stroke were compared using historical data from a random sample of Medicare patients hospitalized for stroke in 1991. Patients in the 2 groups had similar costs for their initial hospitalization and for poststroke months 1 to 3, but in months 4 to 24, total direct medical costs averaged $375 per month more for patients in the recurrent stroke group, even though they had a higher mortality rate. This difference was largely attributable to nursing home care and acute rehospitalization—consistent with recurrent stroke's propensity for causing more severe disability than initial stroke.[6]

## Resource Use and Risk of Recurrent Events

### *Recurrent Events and Hospitalizations*

After an initial stroke, survivors have a substantial risk of recurrence. Pooled data from several US population-based studies found that for initial stroke patients aged 40 to 69 years, the risk of suffering a recurrent stroke within 5 years was 13% for men and 22% for women. For patients ≥70 years, the 5-year risk of recurrent stroke was 23% for men and 28% for women.[3] An estimated 10% to 15% of first ischemic strokes are preceded by a transient ischemic attack (TIA).[3,34,35] Prospective community studies in the United Kingdom have found that ~12% of people who experience a TIA will have a stroke within the first year, and 30% will have one within 5 years.[35] These data suggest that the risk of stroke after a TIA is roughly similar to the risk of recurrence after an initial stroke.

Recently published claims analyses provide additional real-world data on secondary events after a stroke. Vickrey et al[36] used administrative data from several large US managed care organizations, including commercial (employer-based) and Medicare plans, to identify patients who had stroke, acute myocardial infarction (MI), or PAD during 1995-1998. Vickrey et al estimated the occurrences of subsequent vascular events based on an observation period of up to 3 years after the index event (**Table 1**). In the stroke cohort, more than 75% of secondary events were strokes; in the acute MI cohort, more than 75% of secondary events were MIs; and in the PAD cohort, secondary events were somewhat more likely to be MIs than strokes.[36] Caro et al[37] analyzed poststroke hospitalization rates using administrative data from 18,695 patients who received a diagnosis of ischemic stroke (first or recurrent) in Canada during 1990-1995. In a mean follow-up period of 4.6 years, 72.7% of patients were hospitalized at least once. The mean time to first hospitalization was 1.59 years, and the mean length of stay was 13.9 days. Of the 12.5% of patients hospitalized for any reason in the first month after the index stroke, recurrent stroke accounted for 32.8% of hospitalizations and TIA for 5.8%. Rates of hospitalization for recurrent stroke and TIA subsequently decreased, stabilizing in the second year (**Table 2**).[37] Hospitalization costs were highest in the first year after the index stroke, attributable primarily to

**Table 1.** Cumulative Occurrence of Secondary Ischemic Events After Stroke, AMI, or PAD

| | Commercial Sample (mean age, 62 years) | | | | | |
|---|---|---|---|---|---|---|
| | Stroke Cohort (n = 1631) | | AMI Cohort (n = 6458) | | PAD Cohort (n = 5813) | |
| | Type of secondary event (%) | | | | | |
| Time Since Index Event (years) | Stroke | AMI | Stroke | AMI | Stroke | AMI |
| 0.5 | 3.55 | 0.68 | 0.42 | 2.99 | 0.46 | 0.66 |
| 1.0 | 5.31 | 1.26 | 0.64 | 4.02 | 0.76 | 1.53 |
| 2.0 | 7.57 | 2.25 | 1.11 | 6.01 | 1.32 | 2.82 |
| 3.0 | 8.88 | 3.03 | 1.29 | 7.09 | 1.86 | 4.02 |
| | **Medicare Sample (mean age, 80 years)** | | | | | |
| | Stroke Cohort (n = 1518) | | AMI Cohort (n = 2197) | | PAD Cohort (n = 5033) | |
| | Type of secondary event (%) | | | | | |
| Time Since Index Event (years) | Stroke | AMI | Stroke | AMI | Stroke | AMI |
| 0.5 | 3.62 | 0.65 | 0.91 | 4.93 | 0.86 | 0.98 |
| 1.0 | 6.23 | 1.56 | 1.20 | 7.20 | 1.44 | 1.67 |
| 2.0 | 10.77 | 3.39 | 2.90 | 10.59 | 2.42 | 3.66 |
| 3.0 | 12.17 | 5.05 | 4.17 | 12.39 | 3.33 | 4.73 |

AMI indicates acute myocardial infarction; PAD, peripheral arterial disease.
Adapted from reference 36.

recurrent stroke and TIA. In successive years, hospitalization costs for recurrent stroke and TIA decreased substantially, whereas hospitalization costs for other CVD and bleeds remained about the same. The investigators noted that secondary prevention after the index event was suboptimal; with respect to antiplatelet therapy, only 36.0% of patients filled at least 1 prescription for aspirin (ASA), 4.5% for ticlopidine, 1.1% for clopidogrel, and less than 1% for dipyridamole.[37]

These data suggest that TIA and stroke are important risk factors for subsequent stroke and both are indications for secondary prevention. The Canadian study[37] demonstrates that the need for secondary prevention may be greatest in the first 6 to 12 months after an index stroke.

### *Treatment Persistence and Recurrent Events*

Shaya et al[38] used claims data from Medicaid managed care organizations in Maryland to identify patients who had a stroke in 2001-2003. The study included 925 stroke patients who received antithrombotic therapy (ASA, clopidogrel, or warfarin). Patients were considered to have discontinued therapy if they stopped taking the initial drug prescribed (switching to a different drug was classified as discontinuation). A mean follow-up period of 208 days observed that patients who persisted with initial therapy were 1.57 times more likely to avoid a recurrent stroke compared with patients who were nonpersistent ($P$ <.001).[38]

## Pharmacoeconomics of Antiplatelet Therapy for Secondary Stroke Prevention

### *Antiplatelet Options*

The antiplatelet options currently available for secondary prevention of ischemic noncardioembolic stroke include ASA, ASA + extended-release (ER) dipyridamole (DP), and clopidogrel. Ticlopidine, although available, is rarely used today because of its unfavorable adverse effects profile and will not be discussed in this article.

**Table 2.** Hospitalizations for Subsequent Stroke and TIA After an Index Ischemic Stroke

| Time Period | Hospitalizations Due to Stroke | | Hospitalizations Due to TIA | |
|---|---|---|---|---|
| | n (% of all hospitalizations) | Rate (per patient-year) | n (% of all hospitalizations) | Rate (per patient-year) |
| Month 1 | 800 (32.8) | 0.56 | 142 (5.8) | 0.10 |
| Month 2 | 312 (21.4) | 0.23 | 51 (3.5) | 0.04 |
| Months 3-6 | 645 (14.7) | 0.12 | 164 (3.7) | 0.03 |
| Months 7-12 | 433 (8.9) | 0.06 | 152 (3.1) | 0.02 |
| Year 2 | 545 (6.7) | 0.04 | 214 (2.7) | 0.02 |
| Year 3 | 384 (5.6) | 0.03 | 174 (2.5) | 0.01 |
| Year 4 | 344 (5.8) | 0.03 | 102 (1.7) | 0.01 |
| Year 5 | 257 (4.8) | 0.03 | 112 (2.1) | 0.01 |

TIA indicates transient ischemic attack.
Adapted from reference 37.

Although anticoagulants such as warfarin are clearly superior for preventing cardioembolic stroke, they are no longer recommended for preventing noncardioembolic ischemic stroke. This is largely because of the results of 2 randomized trials: SPIRIT (Stroke Prevention in Reversible Ischemia Trial) and WARSS (Warfarin Aspirin Recurrent Stroke Study).

- In SPIRIT, 1316 patients were randomized to oral anticoagulation (international normalized ratio [INR], 3.0-4.5) or ASA (30 mg/day in most cases). The trial was terminated early following the significantly increased occurrence of the primary outcome (composite of vascular death, nonfatal stroke, nonfatal MI, or nonfatal major bleeding) in the anticoagulation group. The excess was attributed to major bleeding, of which 45% was intracerebral.[39]
- In WARSS, 2206 patients were randomized to 2 years of warfarin (INR, 1.4-2.8) or ASA (325 mg/day). Warfarin was associated with an increased risk of minor bleeding compared with ASA, but there was no significant difference between the groups in regard to major bleeding. The investigators concluded that both agents are reasonable alternatives in the doses used but that warfarin is more costly and patients receiving warfarin require close monitoring.[40]

### *Efficacy, Safety, and Tolerability of Antiplatelet Therapy*

The efficacy and safety of antiplatelet therapy were established by the Antithrombotic Trialists' Collaboration (ATC) meta-analysis. This large meta-analysis incorporated 21 randomized trials that compared antiplatelet therapy to a control. Cumulatively, the trials involved 18,270 patients who had a history of stroke (all types) or TIA. Antiplatelet therapy for a mean of 29 months resulted in absolute risk reduction (ARR) of 36 serious vascular events per 1000 patients—primarily reflecting a reduction in nonfatal stroke (ARR, 25 per 1000 patients; $P$ <.0001). There were smaller but significant reductions in nonfatal MI ($P$ = .0009), vascular mortality ($P$ = .04), and all-cause mortality ($P$ = .002). These benefits outweighed the risk of an estimated 1 to 2 additional major extracranial bleeds per year.[41]

Six major randomized trials have studied the comparative efficacy and safety of different antiplatelet regimens used to prevent secondary events in prior stroke patients. Key findings of these trials are summarized briefly below.

- *CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events)*. In patients with atherosclerotic disease (recent ischemic stroke, recent MI, or symptomatic PAD), clopidogrel proved to be more effective than ASA

(325 mg/day) in reducing the composite outcome of ischemic stroke, MI, or vascular death. The reduction was statistically significant only in the subgroup of patients with PAD. Overall, the safety profile of clopidogrel was at least as favorable as that of ASA; clopidogrel was less likely to cause severe bleeding but more likely to cause severe rash.[42]

- *MATCH (Management of Atherothrombosis with Clopidogrel in High-risk Patients)*. For high-risk patients who recently experienced ischemic stroke or TIA, adding ASA (75 mg/day) to clopidogrel did not significantly reduce the composite outcome of ischemic stroke, MI, vascular death, or rehospitalization for an acute ischemic event; nor did it reduce the individual outcome of ischemic stroke. However, ASA + clopidogrel significantly increased the risk of major—and even life-threatening—bleeding.[43]
- *CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance)*. In patients with documented CHD, CVD, or PAD, adding clopidogrel to ASA (75-162 mg/day) was associated with a marginally significant reduction in the composite outcome of MI, stroke, or vascular death. Among the subpopulation of patients with prior stroke, there was a nonsignificant trend in favor of the combination. ASA + clopidogrel, however, significantly increased the risk of moderate bleeding; it also increased the frequency of severe bleeding, but the difference did not reach statistical significance.[44]
- *ESPS-2 (European Stroke Prevention Study 2)*. In patients who recently suffered ischemic stroke or TIA, the risk of stroke (fatal or nonfatal) was significantly reduced by administering either ASA (25 mg twice daily) or modified-release DP, or a combination of the two, compared with placebo. The combination was significantly more effective than either agent alone. ASA-containing regimens significantly increased bleeding frequency, and bleeding was more often severe. Headaches were notably more frequent in patients using ASA-containing regimens and more likely to cause discontinuation than DP-containing regimens.[45]
- *ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial)*. In patients who recently experienced TIA or minor stroke of presumed arterial origin, the combination of ASA (30-325 mg/day) and DP (usually the ER formulation) was significantly more effective than ASA alone in reducing the composite outcome of vascular death, nonfatal stroke, nonfatal MI, or nonfatal major bleeding. In post-hoc analysis, the incidence of stroke as an individual outcome was not significantly reduced. Adding DP to ASA did not significantly increase the risk of major bleeding; however, medication intolerance was more frequent in the ASA + DP group.[46]
- *PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes)*. The results of this randomized controlled trial were announced in May 2008 at the XVII European Stroke Conference. In patients who recently suffered ischemic stroke, rates of recurrent stroke (any type) were not significantly different in patients receiving ASA + ER-DP (25/200 mg twice daily) compared with those taking clopidogrel (75 mg/day). Ischemic strokes were less frequent in the ASA + ER-DP group, while hemorrhagic strokes were less frequent in the clopidogrel group. The benefit-risk ratio in terms of the combination of recurrent stroke and major hemorrhage did not vary significantly between the 2 treatments.[47]

### *Guidelines*

Based largely on the previously mentioned trials, the 2008 update[48] of the 2006 American Heart Association (AHA)/American Stroke Association guidelines for secondary stroke prevention[49] includes the following recommendations for patients who suffer ischemic noncardioembolic stroke or TIA:

- Antiplatelet agents are recommended instead of anticoagulants to reduce the risk of stroke and other cardiovascular events (Class I, Level of Evidence A).
- ASA monotherapy (50-325 mg/day), the combination of ASA + ER-DP, and clopidogrel are all acceptable options for initial therapy (Class I, Level of Evidence A).
- Based on comparative trials, the combination of ASA + ER-DP is recommended over ASA alone (Class I, Level of Evidence B).
- Clopidogrel may be considered instead of ASA alone (Class IIb, Level of Evidence B). Clopidogrel is a reasonable option for patients who are allergic to ASA (Class IIa, Level of Evidence B).
- Adding ASA to clopidogrel increases the risk of hemorrhage. Combination ASA + clopidogrel is not routinely recommended for ischemic stroke and TIA patients unless they

have a specific indication, such as acute coronary syndrome (ACS) or a coronary stent (Class III, Level of Evidence A).

- There is no evidence that increasing the ASA dose can provide additional benefit to patients who suffer a stroke while receiving ASA. Other antiplatelet agents are often considered, but no single agent or combination has been well studied for this patient category.

### *Investigational Agents*

Several new antiplatelet agents—prasugrel, cangrelor, and ticagrelor—are currently under development for use in patients with CHD. These agents demonstrate more potent antiplatelet activity than currently available drugs such as clopidogrel; while this may enhance the efficacy of these drugs, it may also increase the risk of bleeding. Cangrelor and ticagrelor have the advantage of being rapidly reversible, which could help address any increased risk of hemorrhage.[50]

- Prasugrel is a new thienopyridine (chemically related to clopidogrel and ticlopidine) $P2Y_{12}$ receptor antagonist. Prasugrel has completed the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) phase 3 trial, which involved 13,608 patients with ACS who underwent percutaneous coronary intervention (PCI). The patients were randomized to receive either prasugrel (60-mg loading dose, followed by 10 mg/day) or clopidogrel (300-mg loading dose, followed by 75 mg/day). Prasugrel was superior in decreasing the primary outcome (cardiovascular death, nonfatal MI, or nonfatal stroke), largely because of a significant reduction in the incidence of MI. However, prasugrel was associated with significantly more episodes of life-threatening bleeding and major bleeding. In a post-hoc subgroup analysis, patients with previous stroke or TIA demonstrated net harm with prasugrel. For patients in this subgroup, prasugrel provided no additional benefit compared with clopidogrel and was associated with a strong trend ($P$ = .06) toward increased bleeding, including intracranial hemorrhage.[51] These results suggest that prasugrel—at least at the studied dose—should not be used in patients known to have cerebrovascular disease.[52]
- Cangrelor is an intravenous, reversible, nonthienopyridine $P2Y_{12}$ antagonist that has shown promise in patients who have ACS or are undergoing PCI. The CHAMPION-PCI and CHAMPION-PLATFORM are 2 ongoing phase 3 trials that are evaluating cangrelor.[50] Results of cangrelor use in patients with prior stroke have not been reported. As an intravenous agent, cangrelor would not be suitable for long-term secondary prevention but potentially could be used in cases of acute stroke.
- Ticagrelor, a nonthienopyridine, is the first oral reversible $P2Y_{12}$ antagonist. PLATO (Platelet Inhibition and Patient Outcomes) is an ongoing phase 3 trial comparing the use of ticagrelor versus clopidogrel in ACS/PCI patients, with the primary end points of death, MI, and stroke.[50] Results in patients with prior stroke have not been reported.

Given the established cost-effectiveness of ASA monotherapy (50-325 mg/day) and combination therapy with ASA + ER-DP, as well as the quantity of data associated with these 2 options and clopidogrel, any investigational agents will need to show superior comparative efficacy to achieve parity formulary status. Furthermore, such superiority will likely need to be achieved at an equal or only slightly higher price to ensure a positive cost-efficacy outcome. As more agents become available and more existing drugs are offered in generic form, this drug category will become more highly managed, with managed care organizations looking for an opportunity to select preferred therapies.

### *Pharmacoeconomic Analysis*

Multiple cost-effectiveness analyses have been reported from various countries,[53-62] including 4 from the perspective of a US payer.[54,58-60] Of the 4 US studies,[54,59,60] 3 compared all of the AHA/American Stroke Association–recommended antiplatelet regimens. Matchar et al conducted the most recent of these studies, using the Duke Stroke Policy Model (DSPM), a peer-reviewed simulation model of the natural history of stroke and the impact of prevention strategies.[54] Matchar et al compared the cost-effectiveness of ASA, ASA + DP, clopidogrel, and placebo. Using outcomes data from ESPS-2 and CAPRIE, recurrent stroke risk ratios were calculated for ASA versus placebo, ASA + DP versus placebo, and clopidogrel versus placebo (the latter derived from ratios for clopidogrel vs ASA and ASA vs placebo). Stroke care cost estimates were based on Medicare claims data, and quality-adjusted life-years (QALYs) were estimated according to

**Table 3.** Pharmacoeconomic Analysis of Antiplatelet Regimens: Base-case Results

| Treatment | Cost ($) | QALYs | Comparison | Incremental Cost ($) | Incremental QALYs | Incremental Cost-effectiveness ($/QALY) |
|---|---|---|---|---|---|---|
| PLB | 48,405 | 3.54 | | | | |
| ASA | 48,681 | 3.70 | vs PLB | 276 | 0.16 | 1725 |
| CLO | 52,721 | 3.77 | vs PLB | 4316 | 0.23 | 18,765 |
| | | | vs ASA | 4040 | 0.07 | 57,714 |
| ASA + DP | 53,004 | 3.93 | vs PLB | 4599 | 0.39 | 11,792 |
| | | | vs ASA | 4323 | 0.23 | 18,796 |
| | | | vs CLO | 283 | 0.16 | 1769 |

ASA indicates aspirin; ASA + DP, aspirin + dipyridamole; CLO, clopidogrel; PLB, placebo; QALY, quality-adjusted life-year.
Adapted from reference 54.

the results of a large survey of patients at risk for stroke. The following drug costs were based on 2005 prices from a wholesale pharmacy Web site: ASA, $1 per month; clopidogrel, $120 per month; ASA + DP, $120 per month. The target population consisted of 70-year-old men who had suffered a mild stroke.[54]

In the base-case analysis, DSPM was run for 10,000 simulated patients for each treatment strategy. To examine the impact of sampling variability ("probabilistic sensitivity analysis"), this procedure was executed 100 times. To evaluate the robustness of the base-case analysis, several conventional sensitivity analyses were performed: (1) using different risk ratio estimates for ASA from 2 published meta-analyses, (2) using drug costs based on the Federal Supply Schedule (ASA, $0.21/month; ASA + DP, $48/month; clopidogrel, $61/month), (3) assuming that treatment was effective for only 2 years, and (4) incorporating risk ratios for MI (based on clinical trial data).[54]

Any 2 strategies can be compared in terms of their incremental cost-effectiveness ratio (ie, the incremental cost divided by the incremental QALYs). A strategy is considered preferable if it improves outcomes at a reasonable cost. The benchmark or threshold for reasonable cost is commonly considered to be $50,000 per QALY; in this study, the benchmark varied between $10,000 and $100,000.[54] Results of the base-case analysis (Table 3) indicated that (1) ASA was cost-effective compared with placebo, largely because of its low cost; (2) ASA + DP improved outcomes, but at an increased cost; and (3) clopidogrel was dominated.[54]

In the probabilistic sensitivity analysis, clopidogrel was rarely preferred. In the conventional sensitivity analyses, reducing medication cost estimates based on the Federal Supply Schedule made ASA + DP more cost-effective and clopidogrel less so. Assuming that treatment was effective for only 2 years moved both clopidogrel and ASA + DP out of the cost-effective range. The other 2 sensitivity analyses had no substantive impact.[54] The investigators concluded that both ASA and ASA + DP appeared to provide good value compared with placebo, with no clear preference for either one. The more one is willing to pay for improved outcomes, the more likely that ASA + DP will be preferred.[54]

Current 2008 prices for ASA + DP and clopidogrel are somewhat higher than the 2005 values used in the analyses by Matchar et al. In 2008, the average wholesale price for a month's supply of ASA + DP was $167 and $156 for clopidogrel.[63] The current costs of other aspects of stroke care may also differ from the 2005 estimates. Also, the analyses by Matchar et al did not take into account outcomes from ESPRIT, which had not yet been published. A more recent pharmacoeconomic analysis from the United Kingdom that incorporated ESPRIT outcomes concluded that ASA + DP is the preferred treatment for secondary stroke prevention (up to a maximum of 5 years, the treatment duration for patients in ESPRIT).[53] However, this result may

not be applicable to the United States because of differences between the 2 countries' healthcare systems.

The analyses by Matchar et al targeted patients who suffered a mild stroke.[54] There may be other relevant considerations for different patient populations. For example, for patients who experienced a more severe initial stroke, preventing recurrence may be less beneficial in terms of QALYs. Thus, it has been suggested that ASA may be the most cost-effective therapy for patients afflicted with substantial disability after an initial stroke.[64]

For some subgroups of stroke patients, clopidogrel may prove more cost-effective. Analysis of the predefined subgroups in CAPRIE suggests that stroke patients with coexisting PAD may derive more benefit from clopidogrel than from ASA.[42,64] Post-hoc subgroup analyses of CAPRIE further suggest that the absolute benefit of clopidogrel compared with ASA is amplified in patients who are at particularly high risk for ischemic events. This includes patients who have diabetes (especially insulin-dependent diabetes),[65] a history of coronary bypass surgery,[66] or who have already experienced recurrent ischemic events.[67] These subgroups were not predefined, however, and CAPRIE may not have been adequately powered for them.[64] Additional research is needed to determine the cost-effectiveness of clopidogrel in subgroups of very high-risk stroke patients.

## Conclusion

Stroke is a major cause of death, disability, and reduced QOL; it is also among the most expensive diseases in the United States. Patients who experienced an initial stroke or TIA are at increased risk for recurrent events. Recurrent stroke is associated with greater rates of mortality and morbidity and higher costs than initial stroke. Effective secondary prevention of recurrence would substantially improve clinical and economic outcomes.

While anticoagulants constitute an effective prevention for cardioembolic stroke, antiplatelet therapy is indicated for secondary prevention of noncardioembolic ischemic stroke. The ATC meta-analysis established the efficacy and safety of antiplatelet therapy. The current major antiplatelet options are ASA, ASA + ER-DP, and clopidogrel. The comparative efficacy and safety of these agents have been studied in 5 major randomized trials (CAPRIE, MATCH, CHARISMA, ESPS-2, and ESPRIT). Based largely on these clinical trials, the AHA/American Stroke Association established current guidelines for secondary prevention of noncardioembolic ischemic stroke that include these recommendations:

- ASA (50-325 mg/day), ASA + ER-DP, and clopidogrel are all acceptable options for initial therapy.
- ASA + DP is recommended over ASA alone.
- Clopidogrel can be considered as an alternative to ASA and is a reasonable option in patients who are ASA-intolerant.
- The combination of ASA + clopidogrel increases the risk of bleeding and is not routinely recommended for secondary stroke prevention. However, it may be indicated in stroke patients who are at very high risk for coronary conditions.

A recent pharmacoeconomic analysis supported the use of either ASA or ASA + DP for patients whose initial stroke was mild. The base-case analysis concluded that ASA monotherapy was cost-effective compared with placebo, largely because of its low cost. ASA + DP improved patient outcomes compared with ASA alone, but at an increased cost. Clopidogrel was not cost-effective in comparison with regimens of either ASA alone or ASA + DP.

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