Antiplatelet Therapy for Secondary Prevention of Acute Coronary Syndrome, Transient Ischemic Attack, and Noncardioembolic Stroke in an Era of Cost Containment

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Abstract: Physicians are aware of the profound impact of oral antiplatelet therapy for secondary prevention of acute coronary syndrome (ACS), transient ischemic attack, and noncardioembolic stroke. Numerous clinical studies have compared the benefits of aspirin (ASA) alone with those of combination therapy with extended-release dipyridamole or with those of clopidogrel, with or without ASA, for secondary stroke prevention; and of ASA monotherapy compared with ASA plus clopidogrel combination therapy for secondary prevention in various ACS populations. More recently, ASA plus prasugrel has been compared with ASA plus clopidogrel in a high-risk ACS population. However, given the different treatment modalities and methods used in the various trials, it is difficult to make generalizations as to which therapy is most effective with the lowest risk of bleeding. Further complicating physician's decision making are cost considerations, particularly with the newer oral antiplatelet agents, which are considerably more expensive than ASA. This review provides a brief overview of the clinical data on each of the currently marketed oral antiplatelet agents and the available data on cost-effectiveness for the secondary prevention of ACS, transient ischemic attack, and noncardioembolic stroke.

Key Words: anticoagulants, stroke, angina, myocardial infarction, cost-benefit analysis

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Coronary heart disease (CHD) and stroke remain the first and third leading causes of mortality in the United States, respectively, and the first and second leading causes of deaths worldwide, respectively.[1,2]

The economic costs of CHD and stroke are enormous, with an anticipated cost of $250.8 billion in direct and indirect costs for both in 2010 in the United States.[3]

In the United States, an estimated 1.37 million hospitalizations for acute coronary syndromes (ACSs) occurred in 2006, more than half (810,000) of which were for myocardial infarction (MI), and 537,000 of which were for unstable angina.[3] Direct medical costs of ACS are estimated at approximately $75 billion annually, with much of that attributed to inpatient costs. The costs are not limited to a Medicare population; an analysis of costs in a younger managed care population with new-onset ACS identified total health care costs of $309 million, or $22,529 per patient, for an mean follow-up of 292 days after hospitalization or care provided in an emergency department.[4] Overall, medical costs during the first year after a stroke are more than 10 times the cost of the average commercially insured individual.[5]

Although death rates for CHD, including MI, have fallen in the past 40 years, owing in part to significant improvements in treatments and in primary and secondary prevention approaches, the mortality rate is likely to plateau or even rise, given the concurrent epidemics of obesity and diabetes.[1,6] This makes continued improvements in prevention critical.

The incidence and severity of stroke in the United States have also decreased in recent years, also likely owing to improved detection and treatment as well as to early identification of transient ischemic attack (TIA).[7] However, stroke still carries an extremely high mortality rate of 41.6%, with 133,900 deaths in 2007.[1] The mortality rate is highest for hemorrhagic strokes, with 37% to 38% of these strokes resulting in death within 30 days among individuals aged 45 to 64 years, compared with 8% to 12% of ischemic strokes.1 The 1-month mortality rate for ischemic stroke among individuals aged 65 years or older is 8.1%, whereas the rate for hemorrhagic stroke is 44.6%.[2]

Significant opportunities for secondary stroke prevention remain, particularly because approximately half of all strokes that occur in the first week after a TIA occur within the first 24 hours.[8] Appropriate treatment after TIA or stroke could significantly reduce the risk of stroke and its attendant disability and direct and indirect costs.[5,9]

This review provides an overview of major cardiac and stroke trails, which also have separate published papers with economic analyses of their data. We summarize the major antiplatelet agents and the pivotal trials used in their approval for secondary prevention of cardiovascular disease as a foundation for the economic discussion. Clinical effectiveness of these agents is then modeled to project cost-effectiveness. The economic models vary, making comparisons between studies difficult. By presenting a variety of papers, an overall picture of these agents emerges.

THE ROLE OF ORAL ANTIPLATELET THERAPY IN SECONDARY PREVENTION OF ACS, TIA, AND NONCARDIOEMBOLIC STROKE

Oral antiplatelet therapy is a critical component of secondary prevention of ACS, TIA, and noncardioembolic stroke. Currently, 5 oral antiplatelet therapies are available in the US market: aspirin (ASA), combination therapy with extended-release (ER) dipyridamole plus ASA, ticlopidine, clopidogrel, and prasugrel.

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Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of dual antiplatelet therapy with ASA and clopidogrel for all patients with ACS. Although ticlopidine is included in the guidelines, it is rarely used in the United States owing to the high incidence of drug-related hematologic abnormalities.[10] In patients who have had a stroke or TIA, ASA alone or in combination with ER dipyridamole, or clopidogrel, is recommended.[11,12]

The basis for these recommendations is outlined below.

Aspirin

Aspirin selectively and irreversibly inhibits arachidonate cyclooxygenase in platelets, limiting the generation of thromboxane A_2, a key mediator of platelet activation and aggregation. Aspirin has been a mainstay of antiplatelet therapy in both ACS and stroke since the Antiplatelet Trialists' Collaboration demonstrated that it reduced the relative risk of vascular deaths and nonfatal MI.[13] Today, major guidelines recommend its use for secondary prevention in both patients with ACS and patients with a risk of recurrent stroke or other vascular events.[14–16]

A meta-analysis of data from clinical trials, examining the impact of ASA on the risk of serious vascular events and major bleeds in stroke, found that ASA increased the number of major bleeding episodes, both gastrointestinal and extracranial.[17] Therefore, although ASA is exceptionally inexpensive, the bleeding risk must be taken into account based on patients' medical history.

ER Dipyridamole Plus ASA

Dipyridamole inhibits platelet function through several biochemical pathways that ultimately increase platelet cyclic adenosine monophosphate and inhibits cyclic guanosine monophosphate phosphodiesterase, thereby increasing cyclic guanosine monophosphate phosphodiesterase levels.[18] Extended-release dipyridamole plus ASA is indicated to reduce the risk of stroke in patients who have had a TIA or ischemic stroke due to thrombosis.[18] It has not been specifically studied in patients with ACS or MI, although some patients in the stroke trials have a history of MI.

The trial leading to the approval of this combination therapy, Second European Stroke Prevention Study, compared ASA plus ER dipyridamole with either compound alone or with placebo in preventing the primary end points of stroke or death, or of a composite of stroke and death, over 2 years in patients with prior TIA or stroke.

In the study population of 6602 patients, the combination reduced the risk of stroke or death by 24% versus placebo compared with a 13% reduction with ASA alone and a 15% reduction with dipyridamole alone compared with placebo. However, the treatment had no statistically significant effect on all-cause mortality. The most common adverse effect in both groups receiving dipyridamole was headache, whereas all-site and gastrointestinal bleeding were more common in patients receiving ASA than in those receiving dipyridamole.[19]

In the Prevention Regimen for Effectively Avoiding Second Strokes trial, the combination of ASA plus ER dipyridamole was associated with a reduction in the risk of recurrent stroke of similar magnitude to that for clopidogrel. However, the trial was not sufficiently powered to demonstrate superiority or equivalence of either drug. Although more hemorrhagic strokes occurred in the ER dipyridamole plus ASA group than in the clopidogrel group, the net risk for recurrent stroke or major hemorrhagic event was similar and there was no significant difference in the risk of fatal or disabling stroke. More patients permanently discontinued the ASA plus ER dipyridamole treatment than discontinued the clopidogrel treatment because of adverse events, primarily headache, vomiting, and nausea.[20] The combination of ER dipyridamole plus ASA has not been evaluated in patients with ACS.

Although these 2 important trials have demonstrated the effectiveness of combination therapy in stroke prevention, some patients cannot tolerate dipyridamole and the addition of this medication is more cost-prohibitive than ASA alone.

Clopidogrel

Clopidogrel is a prodrug that requires first-pass metabolism in the liver to its active metabolites to exert its antiplatelet effects via inhibition of the P2Y12 adenosine diphosphate receptor.[21] It is indicated for the reduction of thrombotic events in patients with recent MI, recent stroke, and established peripheral arterial disease (PAD). In patients with ACS, clopidogrel is indicated in all patients with ST-elevation myocardial infarction (STEMI) who receive a stent and all patients with non–ST-elevation myocardial infarction (NSTEMI) with or without stent placement.[22] In March 2010, the US Food and Drug Administration announced the addition of a boxed warning to the label of clopidogrel regarding the drug's reduced effectiveness in patients who are poor metabolizers of the drug due to genetic differences in CYP2C19 function.[23]

In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial, clopidogrel alone was compared with ASA alone in reducing the risk of ischemic stroke, myocardial infarction, or death from cardiovascular causes in patients with PAD, a recent stroke, or myocardial infarction. The relative risk reduction was 8.7% in favor of clopidogrel.[24] Subgroup analysis of the trial demonstrated that clopidogrel's effectiveness differed according to the specific vascular bed affected. A nonsignificant improvement over ASA occurred in patients with stroke and MI. The greatest benefit was in the subset of patients who had PAD.

Only one trial has specifically evaluated the use of clopidogrel plus ASA or placebo in patients who had stroke. It examined the incremental effect of ASA versus placebo in patients with prior stroke treated with clopidogrel. The Management of Atherothrombosis with Clopidogrel in High-risk Patients With Recent TIA or Ischemic Stroke trial randomized patients with recent stroke or TIA and at least one other vascular event who were already receiving clopidogrel to receive additional ASA or placebo for 18 months' follow-up.[25] The primary end point was a composite of stroke, MI, vascular death, or rehospitalization for acute ischemia. Results did not differ significantly between groups. The patients receiving ASA had a higher rate of life-threatening bleeding episodes.[25] Thus, although there was no significant difference in the ability of ASA added to clopidogrel to reduce major vascular events, the combination did significantly increase the risk of serious bleeding.

Evidence in support of the use of clopidogrel plus ASA in patients with ACS and in those undergoing percutaneous coronary intervention (PCI) comes from numerous clinical trials[26–31]; however, only Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) is discussed. The CURE trial randomly assigned a little more than 12,000 patients with NSTEMI ACS who presented within 24 hours of symptom onset to receive clopidogrel, 300 mg, immediately, then either clopidogrel (75 mg)/ASA or placebo/ASA for 3 to 12 months. Patients in the clopidogrel group demonstrated a 20% relative risk reduction in the composite primary outcome of death from cardiovascular causes, nonfatal MI, or stroke compared with those in the ASA/placebo group.[32] PCI-CURE evaluated patients with NSTEMI ACS undergoing PCI in the CURE trial.

TABLE 1. Economic Analyses of Antiplatelet Therapy for Secondary Prevention in Patients With ACS or Stable Cardiovascular Disease

Study/Country/Analysis Time Period/Sensitivity Analysis	Source of Clinical Data	Cost Perspective	Cost-Effectiveness of Clopidogrel
Badia et al.[39] (2005) -Lifetime: €30,000 per LYG -Spain -12 months and lifetime analysis period -Outer limits of 95% CI of the relative risk of events	CURE (clopidogrel + ASA vs ASA)	N/A	-12 months: €17,190 per LYG -Clopidogrel added to standard therapy in the first year of treatment is cost-effective
Beinart et al.[40] (2005) -US -12-month period -Bootstrap method (5000 iterations)	CREDO (ASA + clopidogrel 1 month vs ASA + clopidogrel 12 months)	Societal	-Based on Framingham life-expectancy estimation: $3685–$4353/LYG -Based on Saskatchewan life-expectancy estimation: $2929–$3460/LYG -Pretreatment with clopidogrel prior to PCI followed by 1 year of clopidogrel treatment is "highly" cost-effective.
Berg et al.[41] (2008) -Sweden/France/Germany -30 days and 1 year -Bootstrap analysis (1000 replications) and second-order stochastic analysis (1000 simulations)	Meta-analysis of PCI-CURE, CREDO, PCI-CLARITY (to determine effect of clopidogrel on MI and cardiovascular death at 30 days and at end of follow-up at 1 year)	Societal (Sweden) Payer (France/Germany)	-Sweden: pretreatment and long-term treatment = 0.093 QALYs -Germany: 0.090 QALYs; treatment cost €709 more than no treatment, for an ICER of €7871/QALY -France: Pretreatment and long-term treatment: 0.095 QALY. Based on direct medical costs only, incremental cost is €494 euros for clopidogrel, or an ICER of €5226/QALY -Preterm and long-term (1-year) treatment after PCI with clopidogrel are cost-effective
Cowper et al.[42] (2005) -US -12 months -Single and multiway sensitivity analysis	Patients undergoing PCI at Duke University Medical Center from January 1999 to December 2001	Societal	-$15,696/LYG -Clopidogrel treatment for 1 year after PCI is cost-effective
Gaspoz et al.[43] (2002) -US -25 years - Outer limits of 95% CI of the relative risk of events based on the Antiplatelet Trial List	Coronary Heart Disease Model (clopidogrel vs ASA)	Payer	-$11,400/QALY -Monotherapy with ASA or with clopidogrel in ASA-intolerant patients is cost-effective. However, monotherapy with clopidogrel or clopidogrel combination with ASA is not cost-effective in all patients. Combination therapy with clopidogrel and ASA is cost-effective in patients at highest risk. However, as the cost of clopidogrel declines, its cost-effectiveness increases.
Karnon et al.[44] (2005) -UK -Lifetime	Observation study (clopidogrel vs ASA)	Payer	-Clopidogrel: £18,888 /QALY -ASA: £21,488/QALY -Two years of treatment with clopidogrel in patients at risk of secondary occlusive vascular events is cost-effective

-Probabilistic sensitivity analysis using Monte Carlo simulations (1000 simulations)			
Kolm et al.[45] (2007) -Canada -Lifetime -Bootstrap methods with 5000 replicates Cost-effectiveness threshold of $20,000	CURE (clopidogrel + ASA vs ASA in NSTEMI) and PCI-CURE (clopidogrel + ASA vs ASA alone for PCI pretreatment and clopidogrel for posttreatment	NA	-92% of bootstrap replications in CURE <$20,000; -82.2% in PCI-CURE -ICER per event prevented = $12,524/year/CURE; $9250/year/PCI-CURE -ICER per life-years gained = $3856/year/CURE $3763/year/PCI-CURE -Clopidogrel plus ASA is cost-effective compared with ASA alone and with other commonly used cardiovascular therapies
Lamy et al.[46] (2004) -US, UK, Sweden, France, Canada -9 months -Bootstrap analysis	CURE (clopidogrel + ASA vs ASA)	Societal	-US: €25,437 per prevented life-threatening event -UK: €16,847 per prevented life-threatening event -Sweden: €13,857 per prevented life-threatening event -France: €16,186 per prevented life-threatening event -Canada: €5585 per prevented life-threatening event -Overall 2% absolute reduction in total primary events resulted in significant incremental cost-effectiveness ratio similar to those of other antiplatelet options
Lee et al.[47] (2006) -Hong Kong -10 months	Retrospective case review, 54 patients treated with ASA alone compared with hypothetical cohort treated with clopidogrel + ASA	Payer	-Average cost of management: -ASA: $10,940 -ASA + clopidogrel: $10,757 -The overall cost impact of clopidogrel plus ASA was similar to that of ASA monotherapy
Lindgren et al.[48] (2004) -Sweden -12 months -Outer limits of 95% CI of the relative risk of events	CURE (clopidogrel + ASA vs ASA)	Societal	-€1009-€1365 per LYG -Clopidogrel plus ASA "standard therapy," including ASA, is cost-effective
Mahoney et al.[49] (2006) -Early PCI subgroup: $935/LYG -US -12 months	PCI-CURE (clopidogrel + ASA vs ASA) Considered the mpact of clopidogrel on risk of fatal MI only, fatal and nonfatal MI only, and all death	Societal	-Overall: $2856-$4885/LYG
Mahoney et al.[50] (2010) -US -14.7 months	TRITON-TIMI 38 (prasugrel vs clopidogrel in moderate-to-high–risk ACS patients undergoing PCI)	Societal	-Clopidogrel given for up to 1 year after PCI in patients with ACS is a "highly cost-effective treatment strategy" -Prasugrel treatment would reduce costs by $221 per patient and increase life expectancy by 0.012 -At an estimated generic price point for clopidogrel of $1/day, prasugrel was cost-saving over the first 30 days only
-Bootstrap resampling Ringborg et al.[51] (2005) -Sweden -12 months -Probabilistic sensitivity analysis using Monte Carlo simulation (1000 simulations)	CREDO (ASA + clopidogrel 1 month vs ASA + clopidogrel 12 months)	Societal	-€3022/LYG -Long-term treatment (12 months) with clopidogrel plus ASA after PCI is cost-effective compared with 28-day therapy

(continued on next page)

TABLE 1. *(Continued)*

Study/Country/Analysis Time Period/Sensitivity Analysis	Source of Clinical Data	Cost Perspective	Cost-Effectiveness of Clopidogrel
Schleinitz and Heidenreich[52] (2005)	CURE (clopidogrel + ASA vs ASA)	Societal	-$15,400/QALY
-US			-1 year of clopidogrel plus ASA in high-risk ACS patients is cost-effective compared with ASA alone
-Lifetime			
-Probabilistic sensitivity analysis using Monte Carlo simulation (1000 simulations			
Weintraub et al.[53] (2005)	CURE (clopidogrel + ASA vs ASA)	Payer	-$6318/LYG
-US			-Clopidogrel was cost-effective option for patients with ACS
-9 months			
-Bootstrap methods (5000 replicates)			

Parts of this table were reproduced with permission from Cheng.[54]

CAPRIE indicates Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CI, confidence interval; CREDO, Clopidogrel for the Reduction of Events During Observation; ESPS-2, Second European Stroke Prevention Study; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PCI-CLARITY, Percutaneous Coronary Intervention in the Clopidogrel as Adjunctive Reperfusion Therapy; QALY, quality-adjusted life years.

Pretreatment with clopidogrel and ASA before PCI followed by long-term (mean of 8 months) clopidogrel reduced the relative risk of the primary end point of a composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI by 30% compared with ASA plus placebo.[33] Clopidogrel will have a generic formulation in the United States beginning in 2012. How this will affect cost-effectiveness in recurrent stroke prevention remains to be seen. A press release from Astra-Zeneca using European Union labeling of ticagrelor and generic clopidogrel showed a cost-effective gain in quality-adjusted life year in favor of ticagrelor for patients with ACS. Data for this economic substudy were derived from the PLATelet inhibition and patient Outcomes trial.[34]

Prasugrel

Prasugrel is a thienopyridine analog with a similar mechanism of action to clopidogrel, irreversibly inhibiting the binding of adenosine diphosphate receptors to platelets, preventing their activation and reducing platelet aggregation.[35] It is indicated for reduction of thrombotic events in patients with ACS who are to undergo PCI.[36] The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 compared clopidogrel with prasugrel in patients with moderate- to high-risk ACS who were scheduled to undergo PCI. The primary efficacy end point was composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. In the cohort of patients with STEMI alone, the rate of the primary efficacy end point was reduced in favor of prasugrel. In the overall cohort of patients with ACS, greater efficacy of prasugrel came from the reduction in MI in the prasugrel group compared with the clopidogrel group.[30]

However, patients with a previous cerebrovascular event before enrollment in the trial had numerically worse clinical outcomes based on the primary end point, and more frequent bleeding (including intracranial bleeding) than those without a previous cerebrovascular event.[30] Prasugrel carries a black box warning of bleeding risk.[36] Individuals with a history of TIA or stroke should not receive prasugrel.

Ticagrelor

Ticagrelor is an oral antiplatelet that reversibly binds to adenosine diphosphate receptor P2Y12, with evidence of a faster onset and greater platelet aggregation inhibition than that seen with clopidogrel. The PLATelet inhibition and patient Outcomes study compared ticagrelor plus ASA with clopidogrel plus ASA in patients with ACS.[37]

At 12 months, the ticagrelor group demonstrated a 16% relative risk reduction in the primary end point of a composite of death from vascular causes, MI, or stroke (864/9333 end points in the ticagrelor group vs 1014/9291 in the clopidogrel group). Ticagrelor also proved more effective at preventing MI alone and death from other vascular causes but not in preventing stroke alone. There was no significant difference in rates of serious bleeding between the 2 groups, although the ticagrelor group experienced a higher rate of noncoronary artery bypass graft-related major bleeding.[38]

ECONOMIC ANALYSES OF COST-EFFECTIVENESS OF ANTIPLATELET THERAPY FOR ACS AND SECONDARY STROKE PREVENTION

Given the current economic climate and the increased pressure from payers for efficacy as well as cost-effectiveness

in health care, there is a critical need to identify the most cost-effective approaches, whether for treatment or prevention. Although clinical guidelines provide important recommendations regarding treatment modalities, they rarely consider specific costs. Guidelines from the AHA, American Stroke Association (ASA), and the American College of Chest Physicians (ACCP) make few distinctions between the use of ASA with or without ER dipyridamole or clopidogrel in their recommendations for post-TIA/stroke oral antiplatelet therapy. The ACCP guidelines recommend ASA either alone or with ER dipyridamole, or clopidogrel for initial therapy in patients who experienced an ischemic stroke or TIA. They further recommend ER dipyridamole/ASA over ASA alone and clopidogrel over ASA alone based on cost, tolerability, availability, ease of use, and absolute risk. In addition, whereas the AHA/ASA recommendations make no distinction between ASA monotherapy, combination therapy with ER dipyridamole, or clopidogrel monotherapy, they do note the influence that adverse effects, cost, and comorbid illnesses should play in drug selection.[11,12]

Although numerous economic analyses have been conducted on the various antiplatelet agents (Tables 1 and 2), such studies vary widely in their assumptions and models, making comparisons across studies challenging. Tables 1 and 2 provide economic analysis of the major studies used in this paper. Table 1 is focused on cardiac protocols (CURE, Clopidogrel for the Reduction of Events During Observation, etc.), whereas Table 2 is focused on stroke/vascular studies (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, Second European Stroke Prevention Study, etc.). Rather than evaluating actual costs and usage, most project data through various simulations.[60] This requires that they be evaluated individually based on their quality rather than compared with one another.[60] Another limitation to such studies is that the cost of the drug varies significantly depending on the patients' geographic location and insurance program. A factor that

TABLE 2. Economic Analyses of Antiplatelet Therapy for Prevention of Stroke/Vascular Events

Study/Country/Analysis Time Period/Sensitivity Analysis	Source of Clinical Data	Cost Perspective	Cost-Effectiveness of Antiplatelet Agents
Chambers et al.[55] (1999) -UK -5 years -Univariate sensitivity analyses	ESPS-2 (ER dipyridamole 400 mg/d + ASA 50 mg/d vs ASA, dipyridamole, or placebo only)	Societal	Combination prevented 29 more strokes than ASA alone per 1000 patients, at an additional cost of £1900 (1996 values). Cost effectiveness did not exceed £7000 per stroke averted or £11,000 pounds per QALY gained. "The extra costs of treatment are balanced by the savings in future costs of acute care and long-term care of the disabled."
Karnon et al.[44] (2005) -UK -2 years -Probabilistic sensitivity analysis using Monte Carlo simulations (1000 simulations)	CAPRIE (clopidogrel for 2 years followed by ASA for lifetime, or ASA alone)	Payer	-£18,888 /LYG -£21,489/QALY -Clopidogrel is cost-effective in patients at risk of secondary occlusive vascular events
Marissal et al.[56] (2004) -France -2 years -Probabilistic sensitivity analysis using Monte Carlo simulations	ESPS-2 (ASA 50 mg + dipyridamole 400 mg vs ASA alone)	Societal	ASA + dipyridamole: net benefits per avoided stroke recurrence of $23,932 compared with ASA alone, and of $31,555 compared with dipyridamole alone ER dipyridamole/ASA is cost-effective compared with ASA alone and dipyridamole alone
Sarasin et al.[57] (2000) -US -Lifetime	Hypothetical cohort of high-risk patients 65+ years, based on results of CAPRIE and ESPS-2 (clopidogrel 75 mg/d, ASA 325 mg/d or dipyridamole 400 mg/d + ASA, 50 mg/d) High-risk patients 65+ years	Societal	Clopidogrel: ICER <$50,000 up to age 80* $30,000/QALY (ages 65 or 70 years with cost <$3.80) -Clopidogrel vs ASA: ICER >$50,000 -ASA + dipyridamole: greater cost-effectiveness and efficacy than ASA alone (was not compared directly with clopidogrel)
Schleinitz et al.[58] (2004) -US -3 years -Probabilistic sensitivity analyses at the extremes of the 95% CI for each model input -Probabilistic sensitivity analysis using Monte Carlo simulations (1000 simulations)	CAPRIE (ASA vs clopidogrel)	Societal	-PAD: 0.55 QALY increase with clopidogrel; $25,100/QALY -Poststroke: 0.17 QALY increase with clopidogrel $31,200/QALY -Post-MI: 0.26 QALY decrease with clopidogrel -In conclusion, clopidogrel is cost-effective and provides a substantial increase in quality-adjusted life expectancy.
Shah and Gondek[59] (2000) -US -2 years after stroke	ESPS-2 (ASA vs clopidogrel vs ASA/dipyridamole)	N/A	-Cost per stroke averted: Clopidogrel: $161,316; ASA/ER-dipyridamole: $28,472 -ER dipyridamole/ASA is cost-effective compared with ASA monotherapy

*Results highly sensitive to cost of clopidogrel.

may alter prescribing habits is that clopidogrel was set to lose its patent protection in the United States in November 2011, which will significantly change the cost-effectiveness results.[61]

Meta-analyses may be beneficial in evaluating cost-effectiveness. In one meta-analysis of 21 studies, Heeg et al.[62] concluded that "from a purely cost effectiveness" perspective, ASA was always the cheapest, safest, and most effective treatment for the secondary prevention of cardiovascular events, although in higher-risk patients, clopidogrel for 1 or 2 years, either alone or with ASA, was more cost-effective for secondary prevention of ischemic events.[63] Using data from both MI and stroke studies, they also concluded that the combination of ASA and ER dipyridamole for secondary stroke prevention was more cost-effective than ASA alone and, in indirect comparisons, than clopidogrel.[62]

The authors concluded that "the cost-effectiveness of antiplatelets hinges on the patient's initial risk, the risk reduction associated with treatment, and the price of the treatment . . . . Cost-effectiveness of antiplatelets can be optimized by individualizing the treatment decision based on patient risk and expected risk reduction."[62]

It may also be helpful to consider economic analyses used to determine national health plan coverage, such as that of Great Britain. National data from Great Britain compared ASA, ER dipyridamole, and ER dipyridamole plus ASA for the prevention of recurrent stroke, determining that the combination therapy would likely result in "significant health benefits at modest extra costs to health and social services" in the prevention of further stroke and other vascular events when compared with ASA alone, and that dipyridamole alone also seems to be a cost-effective alternative to no treatment in patients who cannot tolerate ASA.[56]

Based on this analysis, Britain's National Institute of Clinical Excellence (NICE), which considers cost-effectiveness in making its recommendations, recommends that ER dipyridamole plus ASA be used as part of the prevention of occlusive vascular events for up to 2 years after an initial ischemic stroke or TIA, followed by long-term treatment with ASA. The NICE also recommends clopidogrel alone as part of prevention of occlusive vascular events in patients who cannot tolerate ASA and who have experienced either an occlusive vascular event or who have symptomatic PAD.[63]

Cheng[54] reviewed multiple cost-effectiveness studies on the use of clopidogrel for secondary prevention of cardiovascular events. She found that in all patients with NSTEMI and in those who received coronary stents, treatment with the drug was cost-effective when used in addition to ASA therapy for up to 12 months.[54] However, it was cost-effective when used for secondary prevention of coronary artery disease only in patients unable to tolerate ASA therapy. The studies she used in her analysis are included in Table 1.

MISSED OPPORTUNITIES IN ACS AND STROKE PREVENTION

Decades of clinical research and pharmaceutical development have resulted in numerous evidence-based recommendations related to the prevention of secondary cardiovascular, cerebrovascular, and peripheral vascular events.[12,64] Yet, as Mosca et al.[65] and Kumar et al.[66] have found, physician's awareness and implementation of national guidelines vary considerably based on physician's specialty, the specific guidelines, patient risk level, and geographic location. For instance, although all major medical organizations recommend the use of antiplatelet agents for patients with ACS, Etemad and McCollam[4] found that the use of antiplatelet therapy in patients after a primary ACS event in a managed care population was only 36%. This was from a retrospective claims analysis of patients from 1999 to 2001. In the Can Rapid Risk Stratification of Unstable Angina Patients Supress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines trial, which evaluated the care provided to 64,775 patients with NSTEMI ACS treated at 350 US hospitals, up to 25% of opportunities to provide guideline-recommended care were missed, particularly the provision of recommended antiplatelet therapy. The authors concluded that a lack of guideline adherence significantly contributed to the rate of inhospital mortality.[67]

The situation is not much better in patients who had stroke, with studies finding adherence rates as low as 53% for antithrombotic therapy.[68] As one researcher wrote in an article evaluating prevention efforts in stroke, ". . . where data are available, all primary and secondary stroke prevention efforts are underused and identify clear areas for improvement."[68] Implementing evidence-based guidelines for stroke and ACS, by contrast, can significantly reduce morbidity and mortality and may reduce costs as well.[69]

CONCLUSION

Acute coronary syndrome and stroke account for most deaths in the United States and worldwide and result in significant morbidity as well as direct and indirect economic costs. A cornerstone of secondary prevention is the appropriate use of oral antiplatelet therapies. Because several efficacious oral therapies are available, the decision of which to use often depends on physician' preference and patient risk factors. The guidelines do not take into account patient costs, geographical considerations, or compliance. It has become increasingly clear that there is not an easy clinical decision rule that can be applied to all patients requiring secondary prevention of ACS, TIA, or stroke. Physicians need to continue to educate themselves on all aspects of health care that may have an effect on patients, including patient compliance, which in turn is often affected by a medication's expense. In this health care environment in which cost-effectiveness trails just behind clinical effectiveness in importance, it is critical that physicians become aware of and consider the economic ramifications of the medication choices they recommend to their patients.

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