

# Trends in Usage of Alternative Antiplatelet Therapy After Stroke and Transient Ischemic Attack

Nancy K. Hills, PhD; S. Claiborne Johnston, MD, PhD

**Background and Purpose**—The effects of alternative antiplatelet agents such as clopidogrel and dipyridamole have been studied in clinical trials and heavily marketed. Because public data on their usage are limited, we examined trends in their prescription after stroke and transient ischemic attack to assess the impact of marketing and trial results.

**Methods**—Between 2001 and 2005, 85 US hospitals prospectively enrolled all patients admitted with ischemic stroke or transient ischemic attack into a registry designed for quality improvement (Ethos). Data on rates of antiplatelet medication usage at discharge were examined over time, and trends were evaluated by the Mantel-Haenszel test.

**Results**—Among 18 020 patients included during the 4-year period, 89% were discharged on antithrombotic medication. Between the first quarter of 2001 and the first quarter of 2004, prescription of clopidogrel-aspirin doubled ( $P<0.0001$  for trend), coincident with publication of results from CURE and CREDO showing efficacy in patients with acute coronary syndromes. Monotherapy with aspirin or clopidogrel decreased concomitantly, and use of dipyridamole-aspirin remained constant. After an increased bleeding risk was reported in the clopidogrel-aspirin arm of the MATCH trial, use of the combination decreased sharply from 31.5% in the first quarter of 2004 to 12.8% in the first quarter of 2005 ( $P<0.0001$ ), while an increase was seen in the use of clopidogrel alone (7.6% to 12.8%,  $P=0.03$ ) and dipyridamole-aspirin (7.4% to 20.2%,  $P<0.0001$ ).

**Conclusions**—Clopidogrel and dipyridamole-aspirin are used frequently after stroke or transient ischemic attack. Use of clopidogrel-aspirin was common in patients with recent ischemic stroke before the publication of MATCH, after which rates dramatically declined and use of dipyridamole-aspirin and clopidogrel alone increased. (*Stroke*. 2008;39:1228-1232.)

**Key Words:** antiplatelet agents ■ antithrombotics ■ stroke ■ transient ischemic attack ■ clinical trials  
■ secondary prevention

Treatment guidelines for stroke and transient ischemic attack (TIA) have recommended antiplatelet therapy to reduce the risk of recurrent stroke and other vascular events.<sup>1–3</sup> However, guidelines have generally left the choice of antiplatelet therapy vague, considering aspirin, clopidogrel, and dipyridamole-aspirin all acceptable treatment alternatives, reflecting the uncertainty of the evidence from clinical trials.<sup>1–3</sup>

Three recent large-scale, randomized trials have examined combination therapy with clopidogrel-aspirin. The CURE trial in 2001 and the CREDO trial in 2002 were each conducted in patients with acute coronary syndromes, and both found that clopidogrel-aspirin reduced the rates of serious vascular events when compared with aspirin alone.<sup>4,5</sup> Results of these trials were widely publicized and marketed, and use of the combination was endorsed in the 2002 American College of Cardiology/American Heart Association guidelines for management of patients with coronary heart disease.<sup>6</sup> Prescription of clopidogrel was observed to increase among patients with acute coronary syndromes at hospital discharge.<sup>7,8</sup> The MATCH trial subsequently com-

pared clopidogrel-aspirin with clopidogrel alone in patients with prior stroke or TIA.<sup>9</sup> The trial was negative, with a nonsignificant reduction in major vascular events with combination clopidogrel-aspirin accompanied by an increased risk of bleeding.

Data on actual usage of antiplatelet agents are limited, particularly for the selection of agents other than aspirin. Thus, trends in usage and the potential impact of clinical trials and marketing have not been evaluated. Using a large, national stroke registry, we sought to assess recent trends in the prescription of antiplatelet agents after stroke and TIA. We sought to define usage of alternative antiplatelet drugs and to examine whether publication of large randomized trials, particularly the MATCH trial, was associated with alterations in usage patterns.

## Methods

This study was sponsored by Sanofi-Aventis; the sponsor was not involved in defining the research question and analysis plan and did not have access to the data or this manuscript before publication. We analyzed data from Ethos, a national Web-based acute stroke registry

Received June 15, 2007; final revision received August 4, 2007; accepted August 22, 2007.

From the Departments of Neurology (N.K.H., S.C.J.) and Epidemiology and Biostatistics (S.C.J.), University of California, San Francisco.

Correspondence and reprint requests to S. Claiborne Johnston, MD, PhD, Department of Neurology, 505 Parnassus Ave, M-798, Box 0114, University of California, San Francisco, CA 94143-0114. E-mail clay.johnston@ucsfmedctr.org

© 2008 American Heart Association, Inc.

*Stroke* is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.107.496729

designed to improve quality of care and track outcomes.<sup>10</sup> From 2001 through 2005, Ethos participants prospectively enrolled all patients admitted with ischemic stroke or TIA, as detailed previously.<sup>11</sup> In brief, 85 hospitals across the United States participated in Ethos, which allowed them to track quality of acute stroke care and compare results against benchmarks generated from national data. These hospitals had a median catchment area of 393 000 (interquartile range [IQR] 223 000 to 799 000), had a median of 326 (IQR 204 to 478) beds, treated a median of 275 (IQR 185 to 407) stroke patients per year, and were 48% academic. All were well equipped to deal with stroke patients: the majority had written stroke guidelines (98%), had a neurosurgeon available within 2 hours (95%), and were able to handle stroke patients 24/7 (99%). Slightly fewer had an onsite stroke team (70%). Participants agreed to include all stroke and TIA admissions during their tenure in the registry. Not all hospitals remained in the registry for the entire 4 years; rather, hospitals joined and left the registry at various times throughout the period of study, with a median duration of participation of 22.6 months (IQR 9.3 to 31.9 months).

Fifty standardized data elements were collected, including demographics, timing of symptom onset and hospital arrival, clinical characteristics, and treatment. Information on prescription of medications at discharge included data on the following antithrombotic agents: aspirin, clopidogrel, dipyridamole, ticlopidine, a combination of extended-release dipyridamole and aspirin (henceforth referred to as dipyridamole-aspirin), and warfarin. Because no information was collected on the presence or absence of atrial fibrillation, we were unable to determine whether warfarin was appropriately prescribed to patients with an indication for an anticoagulant. We therefore report rates of warfarin usage but did not attempt to analyze trends in the usage of anticoagulants during this time.

We first examined rates of overall antiplatelet medication usage at discharge (from hospital, or from the Emergency Department if a patient was not admitted) across all patients in all hospitals and assessed whether patients who received no antithrombotic medication had a documented, valid contraindication to treatment. The following were considered to be valid reasons for nontreatment: bleeding risk, refusal of treatment, allergy to medication, peptic ulcer, terminal status, cancer, and recent or planned surgery. We then defined mutually exclusive antithrombotic categories: aspirin alone, clopidogrel alone, clopidogrel-aspirin, dipyridamole-aspirin, other (including either dipyridamole or ticlopidine alone), and warfarin (alone or in combination with an antiplatelet agent). Usage rates were examined over time, with particular reference to the timing of the publication of results from the CURE,<sup>4</sup> CREDO,<sup>5</sup> and MATCH<sup>9</sup> trials. Trends were evaluated with the Mantel-Haenszel test. All statistical analyses were performed with SAS release 9.1 (SAS Institute, Cary, NC).

We initially included all patients with TIA or ischemic stroke who were discharged alive from any hospital that participated in the registry for any length of time during the years from 2001 through 2005. Chronological time was divided into 3-month segments, and usage of the defined antiplatelet groups was charted at these times. To account for the possibility that trends were influenced by the particular group of hospitals in the registry at given points in time, we repeated analyses including only those hospitals that contributed to the registry both before and after the results of the MATCH trial were published (ie, during the entire year of 2004, at the minimum).

## Results

Eighty-five hospitals contributed a total of 18 953 patients diagnosed with TIA or ischemic stroke during the observation period; 18 020 (95%) were discharged alive and included in these analyses. Of these, 12 930 (72%) were diagnosed with ischemic stroke, and 5090 with TIA. These patients were an average 71.3 ( $\pm$ 13.7) years of age, and 82% were white. Overall during the observation period, 89% of patients received an antithrombotic medication at discharge. Of the

**Table. Demographic Characteristics and Discharge Medication Prescribed**

Characteristic	Total (N=18 020)
Age, mean (SD)	71.3 (13.7)
Women, n (%)	9983 (55.4)
Ethnicity, n (%)	
Non-Hispanic white	14 787 (82.1)
African American	2496 (13.9)
Asian/Pacific Islander	102 (0.57)
Hispanic	147 (0.82)
Other/unknown	326 (1.81)
Academic hospital, n (%)	41 (48.2)
Patients treated in academic hospital, n (%)	10 983 (61.0)
Ischemic stroke, n (%)	12 930 (72.0)
Discharge medication prescribed, n (%)	
None	2012 (11.2)
Valid contraindication to treatment	1276 (63.4)
Aspirin only	4640 (25.8)
Clopidogrel only	1768 (9.8)
Aspirin and clopidogrel	3889 (21.6)
Aspirin and dipyridamole	1795 (10.0)
Other antiplatelet agents	53 (0.3)
Ticlopidine only	32 (0.2)
Dipyridamole only	6 (0.03)
Aspirin and ticlopidine	15 (0.08)
Warfarin*	3863 (21.4)
Months in registry, median (IQR)	22.6 (9.3, 31.9)

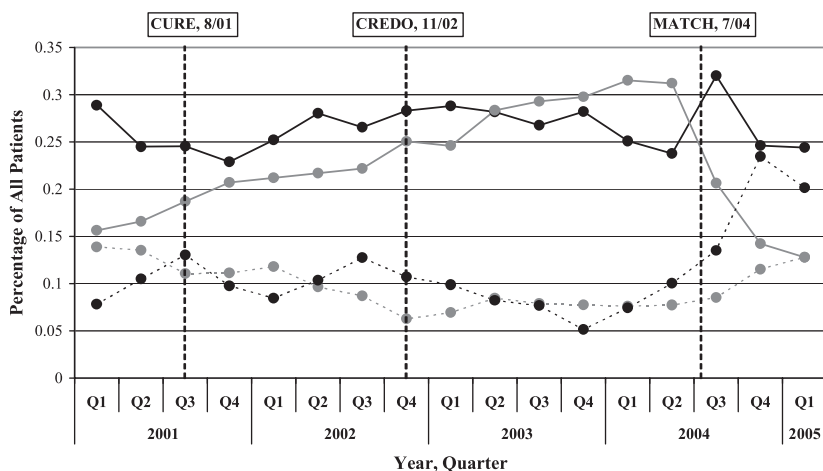
\*Either alone or in combination with antiplatelet(s).

11% who received no antithrombotic medication of any kind, 36% had at least 1 valid documented contraindication to treatment. These included bleeding risk (33% of all contraindicated patients), terminal illness (52%), discharge against advice (4%), surgery (3%), allergy (3%), refusal of treatment (3%), cancer (2%), and ulcer (<1%). Therefore, 93% of eligible patients received antithrombotic treatment.

Aspirin was the most commonly prescribed medication, with a total of 9679 patients (53.7%) receiving it either alone or in combination with another antithrombotic agent. Aspirin alone was prescribed to 26% of patients, 21% received warfarin (with or without additional antiplatelet medication), and 22% were prescribed clopidogrel-aspirin, with  $\approx$ 10% each receiving dipyridamole-aspirin or clopidogrel alone. A very small percentage of patients received either ticlopidine (0.18%) or dipyridamole (0.03%) alone or a ticlopidine-aspirin combination (0.08%) (the Table).

## Combination Therapy With Clopidogrel and Aspirin

Between 2001 and 2002, 2 major randomized, clinical trials reported increased efficacy of clopidogrel-aspirin versus aspirin alone in patients with acute coronary syndromes: the CURE trial in August 2001<sup>4</sup> and the CREDO trial in November 2002.<sup>5</sup> Spanning before and after these trial results were pub-



**Figure.** Trends in antiplatelet usage over time, with reference to 3 large-scale clinical trials: CURE, CREDO, and MATCH. The solid black line represents prescription of aspirin alone, solid gray line represents prescription of aspirin-clopidogrel combination, hatched black line represents prescription of aspirin-extended release dipyridamole, and hatched gray line represents prescription of clopidogrel alone. Q indicates calendar quarter.

lished, the percentage of patients prescribed clopidogrel-aspirin doubled from 15.7% in the first quarter of 2001 to 31.5% in the first quarter of 2004 ( $P<0.0001$  for trend). Monotherapy with aspirin or clopidogrel decreased during this time period, and use of dipyridamole-aspirin remained constant (the Figure).

In July 2004, an increased bleeding risk was reported in the clopidogrel-aspirin arm of the MATCH trial, which specifically evaluated patients with prior stroke or TIA.<sup>9</sup> Concomitantly, the use of the combination after stroke or TIA decreased sharply from 31.5% of patients in the first quarter of 2004 to 12.8% in the first quarter of 2005 ( $P<0.0001$ ). Simultaneously, use of clopidogrel alone increased from 7.7% to 12.8% in this time period ( $P=0.03$ ), while use of aspirin alone, after a sharp rise from 23.8% in the second quarter of 2004 to 32.0% in the third quarter, fell back to 24.4% in the first quarter of 2005. Prescription of dipyridamole-aspirin steadily increased from 7.4% in the first quarter of 2004 to 20.2% in the first quarter of 2005 ( $P<0.0001$ , the Figure).

To account for biases potentially caused by changes in registry membership over time, we repeated analyses including only those hospitals that were in the registry both before and after the MATCH trial results were published (defined here as participation throughout the entire year 2004). Fourteen hospitals met this criterion and contributed a total of 7619 patients. This subgroup was similar in sex and race to the larger cohort, although patients were slightly younger (70.7 vs 71.3 years,  $P=0.0009$ ), were less likely to be treated in an academic hospital (56.6% vs 61.0%,  $P<0.0001$ ), and had a higher percentage of ischemic stroke compared with TIA (73.6% vs 71.8%,  $P=0.003$ ). Median time in registry for these hospitals was 38.1 months (IQR 31.9 to 48.9). Similar to the trend observed in the larger cohort, usage of clopidogrel-aspirin rose from 18% of patients in the first quarter of 2001 to a high of 31.5% of patients in the first quarter of 2004 ( $P=0.0003$  for trend). After the results of the MATCH trial were published, use of the aspirin-clopidogrel combination decreased to 12.8% in the first quarter of 2005, from 31.5% in the first quarter of 2004 ( $P<0.0001$ ). Likewise, usage of aspirin and clopidogrel alone, as well as prescription of dipyridamole-aspirin, increased concomitantly as usage of clopidogrel-aspirin decreased.

## Discussion

In this nationwide registry of patients with ischemic stroke and TIA, we found that alternative antiplatelet agents such as clopidogrel and dipyridamole-aspirin are widely prescribed at hospital discharge. We observed dramatic shifts in usage of these medications coincident with publication of results from large clinical trials.

Guidelines concurrent with our registry data and predating the MATCH trial recommended that every patient with a noncardioembolic stroke or TIA without contraindication should receive an antiplatelet agent to reduce the risk of recurrent vascular events.<sup>1,12,13</sup> We found excellent adherence to this recommendation among hospitals participating in Ethos. Although the guidelines clearly specified the use of antiplatelet therapy, the choice of which therapy to use was left vague, in large part because of the paucity of antiplatelet trials conducted specifically in patients with ischemic stroke or TIA. Any of the following were listed as acceptable treatment options: aspirin (50 to 325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel. The fact that the guidelines themselves did not address the issue of the relative merits of different antiplatelet therapies no doubt contributed to the wide variability in usage that we observed.

During the time period analyzed in the Ethos registry, clopidogrel was the most frequently studied of the alternative antiplatelet medications. Two major trials, CURE<sup>4</sup> and CREDO,<sup>5</sup> compared clopidogrel-aspirin—a promising combination given their different mechanisms of action—versus aspirin alone. These trials included patients with acute coronary syndromes. Despite the fact that stroke was not the disease studied, the positive results may have influenced practice because of the perceived similarity between stroke and coronary heart disease and the lack of alternative therapies. Simultaneously, clopidogrel was being heavily marketed in the US by Sanofi-Synthelabo, in alliance with Bristol-Myers-Squibb. Launched in the United States in 1998 with a sales force of 800,<sup>14</sup> 1155 medical representatives were focusing their efforts on clopidogrel by the year 2000.<sup>15</sup> This number had nearly doubled by the end of 2001.<sup>16</sup> Between the years 2000 and 2004, sales of clopidogrel represented a major source of income for both companies, with average annual growth of 40%.<sup>15–20</sup> By 2004, Sanofi's sales force in the



United States numbered almost 8000,<sup>17</sup> and clopidogrel had become the best-selling product for both companies.<sup>17,21</sup> In the presence of such marketing, it may not be surprising, therefore, that studies of cardiac disease may have influenced the prescribing behavior of physicians for secondary prevention of stroke. Accordingly, the usage of clopidogrel-aspirin, which had begun even before the CURE and CREDO trial results were published, steadily increased during the observation period.

The MATCH trial not only failed to find support for the use of clopidogrel-aspirin in patients with ischemic stroke and TIA, but it also reported a high risk of bleeding in patients treated with this combination.<sup>9</sup> Publication of these results was followed shortly by a dramatic decrease in the use of this combination by hospitals in our study. Clopidogrel monotherapy increased only slightly, most likely because its small advantage over aspirin<sup>22</sup> was counterweighted by its greater cost. Aspirin monotherapy, which had lagged behind prescription of clopidogrel-aspirin before the MATCH trial, rose sharply in the months after the trial but returned to its prior level shortly thereafter. Dipyridamole-aspirin, shown to be more effective than aspirin alone in preventing recurrent events,<sup>23</sup> showed the greatest increase in usage.

Recent guidelines have continued to recommend aspirin, dipyridamole-aspirin, and clopidogrel as acceptable options after stroke or TIA, while recommending against the use of the combination of clopidogrel-aspirin,<sup>2,3,24</sup> in part based on the MATCH results<sup>9</sup> and more recently based on the results of the CHARISMA trial, which showed that clopidogrel-aspirin is no better than aspirin alone in patients with stroke, TIA, and other cardiovascular disease or at high risk for cardiovascular disease.<sup>25</sup> Also, the ESPRIT trial recently demonstrated a reduction in the risk of stroke and cardiovascular events with the use of dipyridamole-aspirin compared with aspirin alone.<sup>26</sup> This also might further alter treatment guidelines and clinical practice.

There are several limitations to our study. Although participating hospitals agreed to enroll all consecutive patients with stroke and TIA, no audit was undertaken to assess whether enrollment at these hospitals was complete, so some selection of cases for inclusion cannot be ruled out. Similarly, the quality of the actual data, which were generally abstracted from medical records, was not evaluated. In terms of prescription of antiplatelet medications, a multitude of factors, including individual hospital practices and broad national trends in stroke care, impact the treatment decisions made by physicians. Although we observed trends in antiplatelet prescription that mirror the findings of large clinical trials during the observation period, we cannot be certain that knowledge of these trials was the driving force behind these trends. In addition, whatever impact the antiplatelet agent trials might have had on prescription practices may appear amplified in our data compared with broader community practice. The Ethos registry was composed primarily of hospitals that are both dedicated to quality improvement and particularly well equipped to deal with stroke; therefore, these hospitals may have been more responsive to new evidence in the literature than the general population of hospitals in the United States. Conversely, these qualities may have engendered more cautious use of clopidogrel-aspirin, given the

limited evidence supporting its use. Roughly half of the Ethos hospitals were academic institutions, compared with about 17% nationally,<sup>27</sup> and academic hospitals may be more likely to respond to research findings than nonacademic hospitals. Last, Ethos hospitals were large and urban, making it difficult to generalize the results of our study to the rural hospitals that comprise 45% of the hospitals in the United States.<sup>27</sup>

Despite these limitations, the data produced in our study are unique and informative. Our data strongly suggest, in a large, nationally distributed sample, that a very high percentage of patients receive some form of antithrombotic therapy after stroke or TIA, with antiplatelet medications other than aspirin in frequent use. Usage of antiplatelet agents other than aspirin appears to have changed as new evidence has become available.

### Acknowledgments

The authors would like to thank Gary Houser and the Stroke Group, Littleton, Colo, which manages the Ethos registry.

### Sources of Funding

This study was funded by an unrestricted grant from Sanofi-Aventis.

### Disclosures

S.C.J. has received research grants from Sanofi-Aventis.

### References

1. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest*. 2001;119:300S–320S.
2. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA, Hankey GJ, Hart RG, Levine SR, Biller J, Brown RD Jr, Sacco RL, Kappelle LJ, Koudstaal PJ, Bogousslavsky J, Caplan LR, van Gijn J, Algra A, Rothwell PM, Adams HP, Albers GW. National Stroke Association Guidelines for the management of transient ischemic attacks. *Ann Neurol*. 2006;60:301–313.
3. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: cosponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:577–617.
4. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
5. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411–2420.
6. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol*. 2002;40:1366–1374.
7. Mehta RH, Roe MT, Chen AY, Lytle BL, Pollack CV Jr, Brindis RG, Smith SC Jr, Harrington RA, Fintel D, Fraulo ES, Califf RM, Gibler WB, Ohman EM, Peterson ED. Recent trends in the care of patients with non-ST-segment elevation acute coronary syndromes: insights from the crusade initiative. *Arch Intern Med*. 2006;166:2027–2034.

8. Tricoci P, Roe MT, Mulgund J, Newby LK, Smith SC Jr, Pollack CV Jr, Fintel DJ, Cannon CP, Bhatt DL, Gibler WB, Ohman EM, Peterson ED, Harrington RA. Clopidogrel to treat patients with non-ST-segment elevation acute coronary syndromes after hospital discharge. *Arch Intern Med*. 2006;166:806–811.
9. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–337.
10. *Ethos Stroke Report and Registry*. The Stroke Group, Littleton, Colo. Available at: <http://thestrokegroup.com>. Last accessed November 20, 2006.
11. Hills NK, Johnston SC. Duration of hospital participation in a nationwide stroke registry is associated with improved quality of care. *BMC Neurol*. 2006;6:20.
12. Wolf PA, Clagett GP, Easton JD, Goldstein LB, Gorelick PB, Kelly-Hayes M, Sacco RL, Whisnant JP. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*. 1999;30:1991–1994.
13. Hack W, Kaste M, Bogousslavsky J, Brainin M, Chamorro A, Lees K, Leys D, Kwiecinski H, Toni P, Langhorne P, Diener C, Hennerici M, Ferro J, Sivenius J, Gunnar N, Bath P, Olsen TS, Gugging M. European stroke initiative recommendations for stroke management-update 2003. *Cerebrovasc Dis*. 2003;16:311–337.
14. *Sanofi-Synthelabo, Annual Report 1999*, Paris, France. Available at: [http://en.sanofi-aventis.com/Images/tytytyty\\_tcm24-10984.pdf](http://en.sanofi-aventis.com/Images/tytytyty_tcm24-10984.pdf). Last accessed July 17, 2007.
15. *Sanofi-Synthelabo, Annual Report 2000*, Paris, France. Available at: [http://en.sanofi-aventis.com/Images/tytytyty\\_tcm24-10979.pdf](http://en.sanofi-aventis.com/Images/tytytyty_tcm24-10979.pdf). Last accessed July 17, 2007.
16. *Sanofi-Synthelabo, Annual Report 2001*, Paris, France. Available at: [http://en.sanofi-aventis.com/Images/tytytyty\\_tcm24-3503.pdf](http://en.sanofi-aventis.com/Images/tytytyty_tcm24-3503.pdf). Last accessed July 17, 2007.
17. *Sanofi-Aventis, Annual Report 2004*, Paris, France. Available at: [http://en.sanofi-aventis.com/Images/050418\\_ar2004\\_en\\_tcm24-2539.pdf](http://en.sanofi-aventis.com/Images/050418_ar2004_en_tcm24-2539.pdf). Last accessed July 17, 2007.
18. *Sanofi-Synthelabo, Business Report 2002*, Paris, France. Available at: [http://en.sanofi-aventis.com/Images/Annual%20Report%202002%20\(Reference%20Document\)\\_tcm24-10974.pdf](http://en.sanofi-aventis.com/Images/Annual%20Report%202002%20(Reference%20Document)_tcm24-10974.pdf). Last accessed July 17, 2007.
19. *Sanofi-Synthelabo, Business Report 2003*, Paris, France. Available at: [http://en.sanofi-aventis.com/Images/en\\_up\\_20040406\\_Annual%20report%202003%20Sanofi-Synthelabo%20\(Reference%20Document\)\\_tcm24-2491.pdf](http://en.sanofi-aventis.com/Images/en_up_20040406_Annual%20report%202003%20Sanofi-Synthelabo%20(Reference%20Document)_tcm24-2491.pdf). Last accessed July 17, 2007.
20. *Bristol-Myers Squibb Company, Annual Report 2003*, New York, NY. Available at: <http://library.corporate-ir.net/library/10/106/106664/items/163923/2003bmsar.pdf>. Last accessed July 17, 2007.
21. *Bristol-Myers Squibb Company, Annual Report 2004*, New York, NY. Available at: <http://www.shareholder.com/visitors/dynamicdoc/document.cfm?documentid=815&companyid=BMJ>. Last accessed July 17, 2007.
22. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348:1329–1339.
23. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study, 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1–13.
24. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004;126:483S–512S.
25. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhilb SR, Weber MA, Brennan DM, Fabry-Ribaud L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
26. Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol*. 2007;6:115–124.
27. Agency for Healthcare Research and Quality. In: Healthcare Cost and Utilization Project (HCUP) Available at: [www.ahrq.gov/data/hcup/#hcup](http://www.ahrq.gov/data/hcup/#hcup). Last accessed Feb. 15, 2006.

## Trends in Usage of Alternative Antiplatelet Therapy After Stroke and Transient Ischemic Attack

Nancy K. Hills and S. Claiborne Johnston

*Stroke*. 2008;39:1228-1232; originally published online March 6, 2008;  
doi: 10.1161/STROKEAHA.107.496729

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2008 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/39/4/1228>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Stroke* is online at:  
<http://stroke.ahajournals.org/subscriptions/>