

## Antithrombotic Utilization Trends after Noncardioembolic Ischemic Stroke or Tia in the Setting of Large Antithrombotic Trials (2002–2009)

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### Abstract

**Background and Purpose**—Several large trials published over the last decade have significantly altered recommended guidelines for therapy following a noncardioembolic ischemic stroke or transient ischemic attack (TIA). The impact of these studies on patient usage of alternative antithrombotic agents has hitherto not been evaluated. We examined the usage of these agents in the United States over the last decade, with regard to the publication of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH), European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), and Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) clinical trials, in order to test the hypothesis that resulting recommendations are reflected in usage trends.

**Methods**—Antithrombotic utilization was prospectively collected as part of the National Ambulatory Medical Care Survey (NAMCS) on a total of 53,608,351 patients in the United States between 2002 and 2009. Patients with a history of ischemic stroke or TIA were included. Patients were excluded if there was a prior history of subarachnoid or intracerebral hemorrhage, or if other indications for antithrombotic treatment were present, including deep venous thrombosis, pulmonary embolism, atrial fibrillation or flutter, mechanical cardiac valve replacement, congestive heart failure, coronary artery disease, peripheral arterial disease, and rheumatoid arthritis. Annual utilization of the following antithrombotic strategies was compared in 53,608,351 patients: 1) aspirin monotherapy, 2) clopidogrel monotherapy, 3) combined clopidogrel and aspirin, 4) combined extended-release dipyridamole (ERDP) and aspirin, and 5) warfarin. Annual utilization was compared before and after publication of MATCH, ESPRIT, and PRoFESS in 2004, 2006, and 2008, respectively. Trend analysis was performed with the Mantel–Haenszel test for trends. Sensitivity analysis of demographic and clinical characteristics stratified by antithrombotic-usage group was performed using the Wald Chi-square test.

**Results**—Utilization of combined clopidogrel and aspirin increased from 3.3% to 6.7% after the MATCH trial ( $p < 0.0001$ ). Following the results of the ESPRIT trial, utilization of combination ERDP and aspirin decreased from 4% to 3% ( $p < 0.0001$ ), utilization of clopidogrel declined from 6.8% to 6% ( $p < 0.0001$ ), and utilization of aspirin remained essentially unchanged. After the PRoFESS trial, utilization of clopidogrel increased from 5% to 9% ( $p < 0.0001$ ), utilization of ERDP-aspirin increased from 3% to 4.6% ( $p < 0.0001$ ), and utilization of aspirin increased from 15.6% to 17.8% ( $p < 0.0001$ ). The proportion of patients on none of the five antithrombotic secondary prevention strategies steadily declined from a peak of 74% in 2003 to 57% by 2009.

**Conclusions**—The impact of the MATCH, ESPRIT, and PRoFESS trials on antithrombotic utilization has been variable. These findings highlight the importance of addressing factors that affect the implementation of findings from major clinical trials.

### Introduction

Antithrombotic therapy has become the cornerstone of secondary ischemic stroke prevention. Over the last decade, three large randomized trials evaluated antithrom-

botic agents for secondary prevention after ischemic stroke or transient ischemic attack (TIA). The “Management of Atherothrombosis with Clopidogrel in High-risk patients” (MATCH) study published in 2004 compared

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the combination of clopidogrel and aspirin with aspirin alone.[1] The “European/Australasian Stroke Prevention in Reversible Ischaemia Trial” (ESPRIT) published in 2006 compared extended-release dipyridamole (ERDP) and low-dose aspirin combination to aspirin alone.[2] The “Prevention Regimen for Effectively Avoiding Second Strokes” (PRoFESS) trial published in 2008 compared clopidogrel to combination ERDP and low-dose aspirin.[3] These results have led to alterations in guidelines for recommended antithrombotic therapy for secondary ischemic stroke prevention, including those published by the American Heart Association/American Stroke Association and the American College of Chest Physicians.[4], [5] However, the impact of these study findings on utilization of antithrombotic agents for secondary stroke prevention has not been assessed. Better understanding of the processes involved in translation of clinical research into practice has been emphasized by several professional organizations.[6] Such information is essential to improve the clinical delivery of proven efficacious treatments for cardiovascular and cerebrovascular diseases. We performed this study in order to understand the nationwide impact of the aforementioned trials on antithrombotic utilization patterns in patients with ischemic stroke or TIA.

## Methods

Antithrombotic utilization in the United States was assessed using data from the National Ambulatory Medical Care Survey (NAMCS).[7] This is an annual survey conducted by the United States Centers for Disease Control and Prevention of patients treated by nonfederally employed ambulatory physicians as classified by the American Medical Association or American Osteopathic Association. Data from the NAMCS has previously been used to assess aspects of ambulatory medical utilization trends in the United States.[8]–[11] The NAMCS uses multistage probability sampling to estimate nationwide ambulatory patient characteristics and medical utilization. Detailed information on the NAMCS sampling design algorithm has been previously published.[12] Survey responses between 2002 and 2009 were obtained for the purposes of our analysis. Data collected included patient demographic information, patient symptoms, office-based treatments rendered and diagnostic procedures performed, diagnoses (converted by NAMCS into ICD-9-CM codes), and medication usage.

Patients at least 18 years of age with a diagnosis of prior ischemic stroke or TIA (ICD-9-CM codes 434.x, 435.x) were selected for analysis. Patients were excluded if they had a history of subarachnoid or intracerebral hem-

orrhage (ICD-9-CM codes 430, 431); probable noncerebrovascular indications for anticoagulation, including deep venous thrombosis (ICD-9-CM codes 453.4x, 453.5x, 453.6, 453.7x), pulmonary embolism (ICD-9-CM codes 415.1x), atrial fibrillation or flutter (ICD-9-CM codes 427.3x), mechanical cardiac valve replacement (ICD-9-CM codes 35.22, 35.24, 35.28), and congestive heart failure (ICD-9-CM codes 428.x); and probable noncerebrovascular indications for maintenance antiplatelet therapy or aspirin use, including coronary artery disease (ICD-9-CM codes 410.x, 411.x, 412, 413.x, 414.x), peripheral arterial disease (ICD-9-CM codes 445.x, 440.2x, 440.3x, 440.4), and rheumatoid arthritis (ICD-9-CM codes 714.x).

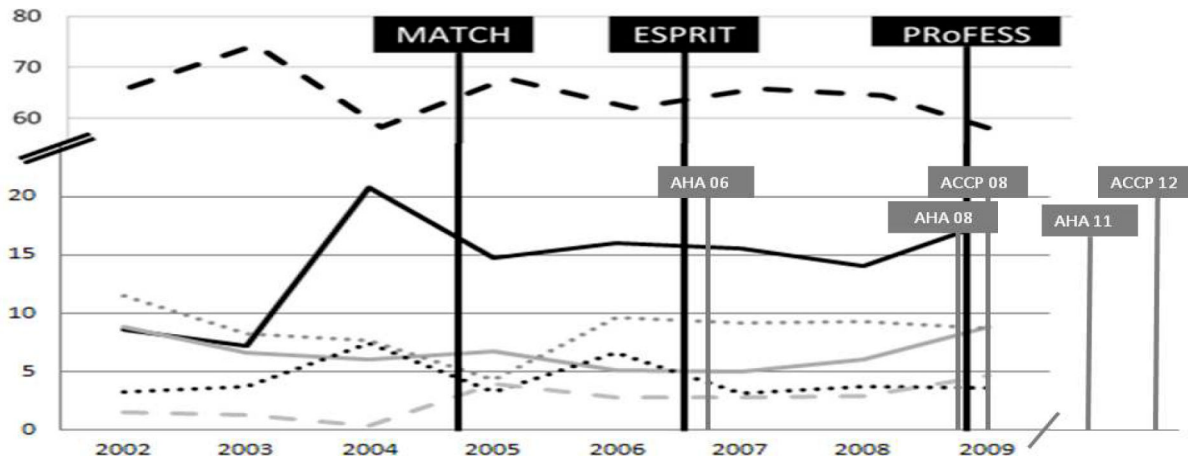
The resulting sample was divided into the following mutually exclusive antithrombotic-usage categories: 1) aspirin monotherapy, 2) ERDP and aspirin combination therapy, 3) clopidogrel monotherapy, 4) clopidogrel and aspirin combination therapy, 5) warfarin monotherapy, and no antithrombotic agent. Usage rates were examined annually, and pre- and post-trial trends were analyzed in reference to the publication years of the MATCH, ESPRIT, and PRoFESS trial results.[1]–[3] Trend analysis was performed with the Mantel–Haenszel test for trends. Sensitivity analysis of demographic and clinical characteristics stratified by antithrombotic-usage group was performed using the Wald Chi-square test. All statistical analyses were performed with SAS release 9.2 (SAS Institute, Cary, NC).

## Results

A total of 53,608,351 patients in the United States between 2002 and 2009 were analyzed. These data were derived from a sample of 2,090 patients using NAMCS multistage probability sampling. Table 1 displays the aggregate national estimates stratified by antithrombotic-usage categories with associated demographic characteristics, medical comorbidities, and third-party payer. Overall, aspirin monotherapy was the most frequently utilized antithrombotic regimen, representing 9,836,739 patients; the least used was combination ERDP and aspirin, representing 2,030,966 patients. We found a significant gender discrepancy between categories: the proportion of women in patients on aspirin monotherapy was high (58%), but was smaller in patients using combination ERDP and aspirin (32%). African-American patients comprised only 4% of aspirin monotherapy users, yet approximately 14% of users of combination clopidogrel and aspirin or combination ERDP and aspirin. Medicare and Medicaid were the most frequent third-party payer sources in all antithrom-

**Table 1. Baseline characteristics of the study patient sample.**

	ASA	Clopidogrel	Clopidogrel-ASA	Warfarin	ERDP-ASA	<i>p</i> -value
Representative sample	9,836,739	4,515,458	2,478,676	4,264,671	2,030,966	
Age (mean)	67.3	69.3	68.5	64.3	68	0.57
Female (%)	57.6	49.9	37.3	47.3	32.1	0.003
Race						
White	80.8	80	79.9	73.4	70.4	<0.0001
Black	4.3	9.4	13.8	11	14.4	
Asian	1.6	7.1	3.4	0.4	7	
Other	13.3	3.5	2.8	15.1	8.2	
Ethnicity						
Hispanic	7.6	7.4	8.8	9.1	5.4	0.83
Non-Hispanic	92.4	92.6	91.2	90.8	94.6	
Third-party payer						
Medicare	61.5	65	50.8	46.2	53.7	<0.0001
Medicaid	4.2	3.7	8.3	0.9	3.2	
Private insurer	29.4	22	33.7	47.9	41.8	
Other	4.8	9.1	7.2	4.9	1.2	
Comorbidities						
Hypertension	61.2	58.7	54.5	50.4	64.8	0.45
Diabetes mellitus	17.5	17.3	27	17.3	11	0.23
Dyslipidemia	39.3	31.6	34.1	31.4	48.2	0.30
Chronic renal failure	0.9	1.1	3.1	0.9	10.7	0.63
Cigarette smoking	18.3	12.1	14.1	9.8	12.7	0.43



**Figure 1. Trends in antithrombotic therapy for secondary ischemic stroke prevention in the United States between 2002 and 2009. the solid black line represents aspirin monotherapy, the solid grey line represents clopidogrel monotherapy, the dotted grey line represents warfarin, the dashed grey line represents ERDP-ASA, and the dotted black line represents clopidogrel-aspirin combined therapy. the large dashed black line at the top represents the proportion of individuals on no defined antithrombotic regimen. Consensus guideline updates from the AHA/ASA and ACCP following publication of each trial are noted via grey vertical labels.**

botic categories with the exception of warfarin users, of which only 47% were participants in either program. Conversely, patients with private health insurance contributed to relatively large proportions of warfarin and combination ERDP and aspirin users (48% and 42%, respectively) compared with users of clopidogrel monotherapy (22%). Annual antithrombotic-usage trends between 2002 and 2009 are shown in Figure 1. The proportion of patients on none of the five antithrombotic secondary prevention strategies declined from a peak of 74% in 2003 to 57% by 2009.

### Utilization Trends Following MATCH

The results of the MATCH trial, published in 2004, demonstrated increased rates of hemorrhage without associated significant reduction in either the secondary endpoint of ischemic stroke or the composite primary endpoint of ischemic stroke, vascular death, myocardial infarction (MI), or acute ischemia hospitalization for patients taking combination clopidogrel-aspirin relative to those on aspirin alone.[1] Compared with the two years prior to publication of trial results, there was an overall increase in utilization of the dual antiplatelet therapy from 3.3% to 6.7% by 2006 following publication of the results of MATCH ( $p < 0.0001$  for trend).

Thereafter, from 2007 to 2009, the use of combination clopidogrel-aspirin decreased to a steady annual rate between 3% and 4%.

### Utilization Trends Following ESPRIT

Results of the ESPRIT trial were published in 2006. ESPRIT demonstrated a reduction in both ischemic stroke, and a composite of stroke, MI, major bleeding, or vascular death with use of combination ERDP, and aspirin relative to aspirin alone.[2] Despite the positive study findings, the use of combination ERDP-aspirin declined from 4% in 2004 to 3% by two years after publication ESPRIT ( $p < 0.0001$  for trend). During the same four-year period, monotherapy aspirin use remained steady (14.7%–14.1%), while clopidogrel use declined from 6.8% to a 2007 nadir of 5% before increasing to 6% by 2008 ( $p < 0.0001$  for trend).

### Utilization Trends Following PRoFESS

The PRoFESS trial results, published in 2008, demonstrated no difference in prevention of ischemic stroke, MI, and vascular death among patients taking clopidogrel versus those taking combination ERDP-aspirin.[3] By the following year, utilization of clopidogrel had increased to 9% compared with 5% the year prior to publication of the results ( $p < 0.0001$  for trend). During the same period, both aspirin monotherapy and combination ERDP-aspirin utilization increased from 15.6% to almost 18% and from almost 3% to 4.6%, respectively ( $p < 0.0001$  and  $p < 0.001$  for trend, respectively).

## Discussion

Our findings demonstrate that shifts in relative antithrombotic agent utilization for secondary ischemic stroke prevention were of variable magnitude subsequent to publication of the MATCH, ESPRIT, and PRoFESS trial results. The expected impact was an increase in utilization of combination ERDP-aspirin and clopidogrel monotherapy with a corresponding decrease in utilization of aspirin among patients with noncardioembolic ischemic stroke or TIA. There was a small decrease in combination ERDP-aspirin utilization following publication of ESPRIT that demonstrated superiority of ERDP-aspirin combination relative to aspirin monotherapy.[2] There was a gradual decrease in the proportion of individuals not using antithrombotics for secondary ischemic stroke prevention during the study period, particularly between 2005 and 2009. This decrease is likely due to an increasing focus on the role of antithrombotic agents for secondary ischemic stroke prevention in guidelines. The prevalence of 55%–65% of patients on no antithrombotic therapy during our study period ini-

tially seems surprisingly high. However, the examination of antithrombotic discharge regimens following admission for ischemic stroke or TIA from 2001 to 2005 reported 11% of patients discharged on no antithrombotic regimen.[13] Several previous investigations have demonstrated antithrombotic nonutilization rates from 67% to 87% at 1 year.[14], [15] Moreover, other studies have demonstrated a progressive decline in medication adherence for secondary cardiovascular event prevention.[16] These findings are consistent with the relatively high proportion of patients on no antithrombotic regimen in our study.

Serendipitously, the studies in our time frame include each of the three possible outcomes from a direct comparison study: 1) one agent causing greater harm, 2) greater benefit, and 3) no appreciable difference in relation to a comparison group. Hills and Johnston found a consistent increase in discharge prescribing of combination clopidogrel and aspirin among patients admitted with an ischemic stroke or TIA from 2001 to 2005, encompassing the 2004 publication of the results of MATCH.[13] This increase was attributed to the publication of CURE and CREDO: both found a significant reduction in the combined endpoint of MI, vascular death, or stroke with the use of prolonged combination clopidogrel and aspirin in the setting of acute coronary syndrome.[17], [18] Following publication of the MATCH trial results, combination clopidogrel, and aspirin prescribing fell substantially: from 31.5% in the second quarter of 2004 to 12.8% by the first quarter of 2005. By contrast, we found an overall increase in combination clopidogrel-aspirin usage from 3.3% to 6.7% between 2003 and 2006, with a decline to a stable usage rate of between 2.7% and 3.7% between 2007 and 2009. This decline in usage temporally correlates with the publication of new guidelines by the AHA/ASA and ACCP (2006 and 2008, respectively) advising against the use of combination clopidogrel and aspirin.[19], [20] This differing pattern of combination of clopidogrel and aspirin utilization likely highlights the relative impact of guidelines. Physicians treating acute ischemic stroke patients would be more likely to specialize in neurology or vascular neurology, and would more likely be aware of the results of individual studies. However, since most ambulatory care is provided by internists or primary care physicians, multidisciplinary consensus guidelines likely have greater impact on ambulatory care practices. The stabilization in combination clopidogrel and aspirin utilization after 2006 is more difficult to explain. One possibility is the carryover influence of other antithrombotic trials. The CHARISMA trial evaluated combination clopidogrel and aspirin in patients with symptomatic coro-



nary, peripheral vascular and cerebrovascular disease, and patients with atherothrombotic risk factors.[21] The results, published in 2006, demonstrated a trend toward reduction of the composite primary outcome of MI, stroke, and vascular death. Likewise, the results of the FASTER study, published late 2007, demonstrated a nonsignificant reduction in stroke within 90 days from initial TIA or ischemic stroke.[22]

The lack of major changes following these trials may be attributed to the delay in updating guidelines for secondary prevention of ischemic stroke. Recommendations from both the American Heart Association/American Stroke Association and the American College of Chest Physicians predating the 2004 MATCH trial did not specifically comment on the combination of clopidogrel and aspirin for secondary ischemic stroke prevention.[23], [24] By contrast, the 2006 AHA/ASA and the 2008 ACCP guidelines both strongly recommended against usage of the combination of clopidogrel and aspirin for secondary prevention.[19], [20] The publication of ESPRIT led to a modest change in recommendations for combination ERDP-aspirin: prior to ESPRIT both the 2006 AHA/ASA and the 2004 ACCP guidelines favored ERDP-aspirin over aspirin monotherapy, based largely on the 1996 ESPS-2 results.[19], [24], [25] The 2008 AHA/ASA guidelines update strongly recommended ERDP-aspirin as first-line therapy, upgrading its strength of recommendation from the previous Class IIa to Class I, its highest grade.[26] Likewise, the 2008 ACCP guidelines strengthened its recommendation of ERDP-aspirin from 2A (“intermediate-strength recommendation”) to 1A (“strong recommendation”).[20] Based primarily on the CAPRIE study,[27] the 2006 AHA/ASA, 2008 AHA/ASA, and 2008 ACCP guidelines suggested clopidogrel over aspirin.[19], [20], [26] Following the PROFESS trial results, the 2011 AHA/ASA guideline position moved to equipoise between clopidogrel monotherapy, combination ERDP-aspirin, and aspirin monotherapy.[4] The 2012 ACCP guidelines continue to suggest clopidogrel usage over aspirin, and maintain equivalence between clopidogrel and combination ERDP-aspirin.[5]

Side effects also influence antithrombotic adherence. [28]–[31] Nonadherence is more common in routine practice due to less rigorous adverse event monitoring. Patients taking ERDP-aspirin often develop significant headache.[32] A meta-analysis of seven randomized-controlled trials found a significantly higher rate of headache in patients taking dipyridamole or ERDP-aspirin compared with controls.[33] Subjects in ESPRIT taking dipyridamole-aspirin discontinued study drug use

almost three times more often than those taking aspirin, and headache was a contributing factor in treatment discontinuation in 26% of those on combination therapy compared with none on aspirin monotherapy.[2] Our findings of an overall modest decrease in ERDP-aspirin usage from 4% in 2005 to 2.9% in 2008, followed by a similarly modest increase to 4.6% by 2009, likely reflect this relatively low tolerability despite the findings of ESPRIT. The increase after 2008 may also reflect the 2008 publication of the AHA/ASA and ACCP guidelines, which were the first updates following ESPRIT.

Another important factor in antithrombotic choice is cost.[31], [34], [35] A 2011 review found that the average monthly cost was \$1 for aspirin, \$247 for ERDP-aspirin (marketed as Aggrenox), and \$214 for clopidogrel (marketed as Plavix).[36] The percentage of Americans on a private health insurance plan decreased annually from 72% in 2000 to 64% by 2010.[37], [38] The percentage of Americans without health insurance increased from 14% in 2000 to 16% by 2010. Concurrently, patients on employer-sponsored private health insurance plans, the most common type of private health insurance, have seen an increase in out of pocket prescription drug costs. From 2001 to 2004, the mean generic drug copayment increased by 43%, the mean copayment for preferred brand-name drugs increased by 61.5%, and the mean copayment for non-preferred brand-name drugs by 94%.[39] Furthermore, most private health insurance plans have increasingly instituted graduated prescription cost-sharing to customers by stratifying brand-name medications into copayment tiers. Plans of three or more tiers increased from 27% in 2000 to 77% by 2011.[39]–[41] Medicare introduced prescription drug coverage in 2003 via Medicare Advantage and Part D.[42] By 2010, 60% of all Medicare Beneficiaries were enrolled one of the two drug coverage plans. Most Medicare Part D plans employ a gap in drug coverage above an initial annual threshold and below an annual limit known as the “donut hole.” A 2007 analysis found that 26% of enrollees were in the donut hole, yet only 4% qualified for marginal catastrophic coverage.[43] An association between increasing drug copayments and drug discontinuation has been previously reported.[35] Thus, the inhibitory factor of cost could partially explain the muted usage response to the results of ESPRIT, and the persistent higher usage of aspirin over clopidogrel and combination ERDP-aspirin.

There are several limitations to our findings. Since the NAMCS is an annual random survey of physician offices across the nation, it is not possible to stratify patient data by time interval between survey and last ischemic

event. Therefore, we were unable to determine whether usage patterns were predominantly affected by the findings of MATCH, ESPRIT, and PRoFESS in patients with recent ischemic events. For the same reason, we also could not confirm our suspicion that patients with more distant ischemic events were more likely to be prescribed aspirin. Second, the chart survey design of the NAMCS allows for the possibility of errors in patient data reporting, including omitting, incorrectly reporting relevant data on diagnoses, and medication usage. However, the practice of obtaining patient information from health practitioners instead of patients probably minimizes such errors. Because our study period is limited to 2009, we cannot assess the delayed effect of PRoFESS, the 2011 AHA/ASA guidelines, and the 2012 ACCP guidelines. We were unable to analyze certain factors such as obesity due to inadequate sampling. Finally, our data is a measure of patient medication usage as reported by their physicians, rather than true medication adherence.

In conclusion, our analysis of nationwide ambulatory antithrombotic utilization for secondary ischemic stroke prevention demonstrated small magnitude changes following publication of results of MATCH, ESPRIT, and PRoFESS. We also noticed a greater correlation between changes in patterns of antithrombotic agents and recommendations provided by AHA/ASA and ACCP guidelines compared with publication of trial results. Further investigation of the causes and clinical consequences of such gaps in clinical trial translation is needed.

## Disclosures

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