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REVIEW

Review and Management of Side Effects Associated with Antiplatelet Therapy for Prevention of Recurrent Cerebrovascular Events

Robert Guthrie

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ABSTRACT

The risk of secondary events following noncardioembolic ischemic stroke or transient ischemic attack (TIA) is high and especially pronounced in the first days and weeks following the initial event; to reduce this risk, it is recommended that antiplatelet therapy be initiated immediately. Although the risk and impact of antiplatelet-associated side effects are generally far less substantial than those of secondary events, some (especially bleeding) can be severe and even life-threatening, and others may reduce adherence to antiplatelet regimens. Therefore, clinicians should implement strategies to reduce the risk of side effects and to manage those that occur. Three antiplatelet regimens have demonstrated substantial reductions in secondary event risk and are currently recommended by consensus panels: aspirin monotherapy at 50-325 mg/day; the combination of aspirin plus extended-release dipyridamole (ER-DP); and clopidogrel monotherapy. Bleeding is potentially the most significant antiplatelet-associated side effect. As bleeding risk with aspirin monotherapy is dose dependent, while preventive efficacy appears similar at all doses above 50 mg/day, aspirin doses should be kept as low as possible. Clopidogrel bleeding risk is similar to aspirin, although a reduced incidence of gastrointestinal bleeding events suggests lower gastrotoxicity. Clopidogrel should not be combined with aspirin after stroke or TIA, as the combination increases bleeding risk without improving antiplatelet efficacy. Patients should be assessed for bleeding risk (especially gastrointestinal bleeding) before initiating antiplatelet therapy; those at elevated risk should be made aware of the signs and symptoms of bleeding events to facilitate prompt treatment. The addition of ER-DP to aspirin does not increase bleeding risk, although ER-DP is associated with risk of headache, which may be severe. The prevalence of headache drops rapidly following initiation of ER-DP, suggesting most patients are able to "push through" this side effect; for those who find headache intolerable, short-term use of a reduced-dose regimen may be helpful.

Robert Guthrie (✉)
Ohio State University, 1380 Edgehill Road, Columbus, OH 43212, USA. Email: Guthrie.1@osu.edu

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INTRODUCTION

Patients who have experienced an ischemic cerebrovascular event, including stroke or transient ischemic attack (TIA), are at extremely high risk for recurrent ischemic events. Of the approximately 795,000 strokes that occur annually in the United States, an estimated 185,000 (~23%) are secondary events incurring significant mortality and morbidity.[1,2] Given the estimated annual direct and indirect costs of US $73.7 billion attributable to stroke overall, direct and indirect costs associated with secondary events are likely to be in the range of US $15-$20 billion annually.[1]

Longitudinal studies have made clear that the risk of a secondary cerebrovascular event following a TIA is at least as great as that following a stroke. The risk following both types of events is heavily front-loaded, with the highest risk during the first few days after the primary event.[3,4] It should be noted that a consensus panel established by the American Heart Association/American Stroke Association (AHA/ASA) has developed a new "tissue-based" definition for TIA, as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction."[3] This replaces earlier symptom- and/or symptom duration-based definitions (eg, transient symptoms with a maximum duration of 24 hours), and by extension likewise redefines ischemic stroke as an infarction of central nervous system tissue.[3] Although the proposed redefinition may slightly affect estimations of secondary stroke risk following the two types of ischemic cerebrovascular events, there is no doubt that both TIA and stroke carry significant short-term risk, and that preventive strategies should be implemented as soon as possible after the initial event.[3-6]

In addition to lifestyle modifications and other steps to reduce overall cardiovascular and cerebrovascular risk (including treatment, if required, for hypertension and hyperlipidemia), the primary therapeutic approach for prevention of secondary cerebrovascular events is the use of antiplatelet therapy.[2] The principal exception is following a primary event of known or strongly suspected cardioembolic origin (eg, in patients with atrial fibrillation or valvular disease),[2] for which anticoagulant therapy provides significantly greater efficacy than antiplatelet treatment. (This article will not address anticoagulant therapy for such patients, and will focus exclusively on antiplatelet therapy.)

Although generally safe and well tolerated, antiplatelet regimens recommended for secondary cerebrovascular event prevention are, as with any therapy, associated with side effects. It must be emphasized that the risks and severity of antiplatelet therapy-associated side effects are far less substantial than those of secondary stroke resulting from failure to apply such therapy. Nevertheless, some side effects of antiplatelet therapy may be potentially life-threatening (primarily bleeding events), while even the less serious side effects may also affect patient adherence. For these reasons, it is important to minimize the risk of antiplatelet-associated side effects and to effectively manage them if they do occur. The great importance of antiplatelet therapy for all patients following a cerebrovascular event requires clinician awareness of both its efficacy and the risk of adverse events. This article reviews the efficacy and incidence and severity of side effects associated with antiplatelet therapy for secondary stroke prevention, and discusses management approaches to reduce their risk and severity.

TEMPORAL PATTERNS OF SECONDARY CEREBROVASCULAR EVENTS

The degree of risk for secondary events after ischemic stroke or TIA has been addressed by

a number of longitudinal studies.[6-8] As noted previously, changing definitions of TIA may affect precise calculations of risk; in addition, some early studies excluded recurrent stroke occurring within a specific time frame after a primary event, especially in the same vascular bed, resulting in underestimated recurrence risk.[6] The overall clinical picture emerging with recent studies consistently demonstrates high risk that is heavily skewed toward the first days after an initial event.

The overall risk of recurrent events or mortality following ischemic stroke was recently assessed in a study of Medicare recipients.[9] Among patients who survived the hospital stay for the initial event, the adjusted 30-day, 90-day, and 1-year risks of rehospitalization were 14.2%, 29.2%, and 55.3%, respectively, while the risks of combined death or rehospitalization were 21.1%, 36.8%, and 61.7%, respectively.[9] There was substantial hospital-to-hospital variation in these rates; when hospitals were ranked by rates of secondary events, the 30-day risk of rehospitalization, for example, was 9.1% for hospitals in the 10th percentile and 19% for those in the 90th percentile.[9] Although the study was not designed to evaluate the relationship between care provided at the initial event and the risk of recurrence, the authors suggest that much of the variance may be attributable to differences in such care (academic centers in the Northeast and West had somewhat better outcomes).[9]

One UK study found recurrence risks of 14.5% and 18.3% for two clinical populations in the 90 days following a first-ever ischemic stroke, with more than half of the recurrent strokes occurring within the first 10 days.[6] A US study found that 10.5% of patients admitted to an emergency department with a diagnosed TIA experienced a stroke within 90 days, with more than half of the events (91/180) occurring within 2 days.[7] Similarly, another study found that the cumulative risk of stroke following a first-ever TIA was 8.6% within the first 7 days and 12% within 30 days.[8]

In an integrated analysis of two longitudinal studies and two clinical trials, it was found that 43% of stroke patients had experienced their most recent TIA 0-7 days prior to the stroke; 9%, 3%, 3%, and 43% experienced their most recent TIA 8-14, 15-21, 22-28, and >28 days, respectively, prior to their stroke. A similar pattern emerged when the intervals between stroke and first-ever TIA were examined, with 30%, 6%, 3%, 2%, and 59% experiencing intervals of 0-7, 8-14, 15-21, 22-28, and >28 days, respectively.[4]

RECOMMENDED ANTIPLATELET REGIMENS: EFFICACY AND SIDE EFFECTS

The antiplatelet regimens currently recommended by AHA/ASA and the American College of Chest Physicians (ACCP) for prevention of secondary cerebrovascular events following noncardioembolic stroke or TIA include aspirin monotherapy at dosages of 50-325 mg/day, the combination of aspirin plus extended-release dipyridamole (ER-DP), and clopidogrel monotherapy. The aspirin plus ER-DP combination is considered by the ACCP preferable to aspirin alone, based on superior efficacy as demonstrated in the second European Stroke Prevention Study (ESPS-2).[2,5,10,11] The combination of aspirin and clopidogrel is not recommended for most patients with recent stroke or TIA, as this combination substantially increases bleeding risk and does not improve preventive efficacy. This combination may be used with caution, however, in patients with recent myocardial infarction, acute coronary syndrome, and/or coronary stent placement.[2,10] Ticlopidine, a thienopyridine related to clopidogrel, has also demonstrated efficacy in

preventing secondary stroke; however, it is only rarely used today because of an unfavorable adverse event profile, including neutropenia and thrombotic thrombocytopenia purpura.[2]

Aspirin Monotherapy

The efficacy of aspirin in preventing secondary cerebrovascular events was established in a series of clinical studies conducted about 20 years ago: the Swedish Aspirin Low-Dose Trial (SALT), the Dutch TIA trial, and the UK-TIA trial, which used aspirin doses ranging from 30 mg/day to 1200 mg/day.[2,10,12-14] The placebo-controlled SALT and UK-TIA studies demonstrated that aspirin at all tested doses reduced the risk of both stroke and mortality by approximately 15%-20%. There was no evidence of any dose-response relationship with respect to preventive efficacy at aspirin doses ≥30 mg/day.[2,10,12-14] These results were also consistent with those observed in the aspirin monotherapy arm of the ESPS-2 study.[11]

In both the UK-TIA and Dutch TIA studies, each of which evaluated two doses of aspirin, the most frequent adverse events involved upper gastrointestinal symptoms (eg, nausea, abdominal pain, vomiting). In the UK-TIA study, upper gastrointestinal symptoms were reported by 41%, 31%, and 26% of patients receiving 1200 mg/day aspirin, 300 mg/day aspirin, and placebo, respectively, while in the Dutch TIA study they were reported by 11.4% and 10.5% of patients receiving 283 and 30 mg/day aspirin, respectively.[12,14]

From a clinical standpoint, bleeding, which may be life-threatening, is the most significant adverse event associated with aspirin therapy. In the UK-TIA study, bleeding symptoms were reported by 9.4%, 7.4%, and 3.4% of patients receiving 1200 mg/day aspirin, 300 mg/day aspirin, and placebo, respectively.[14] In the Dutch TIA study, bleeding symptoms were reported by 8.7% and 6.4% of patients receiving 283 and 30 mg/day aspirin, respectively; major bleeding complications (including fatal bleeds) were reported by 3.4% and 2.6%, respectively.[12]

Therefore, although higher aspirin doses did not demonstrate improved efficacy, there was a clear dose-response relationship with respect to the most important side effects of aspirin monotherapy, namely gastrotoxicity and bleeding. For this reason, current AHA/ASA and ACCP recommendations emphasize the use of lower doses (50-325 mg/day) for aspirin monotherapy.[2,10]

Clopidogrel Monotherapy

The ability of clopidogrel to prevent secondary cerebrovascular events and other cardiovascular events was first demonstrated in the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) study, which enrolled patients with a recent myocardial infarction, ischemic stroke, or peripheral arterial disease. Among patients with recent stroke, clopidogrel demonstrated nonsignificant reductions versus aspirin with respect to recurrent stroke (relative risk reduction [RRR], 8%; 95% confidence interval [CI]: –7-21; P=0.28) and the composite outcome of ischemic stroke, myocardial infarction, and vascular death (RRR, 7.3%; 95% CI: 5.7-18.7; P=0.26).[10,15] The 2008 ACCP guidelines suggest consideration of clopidogrel monotherapy over aspirin monotherapy (grade 2B recommendation, primarily on the basis of CAPRIE), but acknowledge a low level of supportive evidence with respect to the superior efficacy of clopidogrel.[10] However, the 2010 AHA/ASA recommendations consider aspirin monotherapy, aspirin plus ER-DP, and clopidogrel monotherapy to be acceptable options, and consider the level of supportive evidence to be less compelling for clopidogrel (level 2b) than for aspirin or aspirin plus ER-DP

(level 1). The AHA/ASA recommendations also note that with respect to secondary stroke prevention, "No studies have compared clopidogrel with placebo, and studies comparing it with other antiplatelet agents have not clearly established that it is superior to or even equivalent to any one of them."[2]

The adverse event profile of clopidogrel is similar to that of aspirin, although it appears to be less gastrotoxic. In CAPRIE, upper gastrointestinal symptoms were reported by significantly fewer patients receiving clopidogrel (15.01%) than those receiving aspirin (17.59%; $P<0.05$ for between-group comparison); these symptoms were rated as severe in 0.97% and 1.23%, respectively (P=nonsignificant [NS]).[15] However, the incidence of bleeding symptoms was similar between groups (9.27% vs. 9.28%, respectively; P=NS), as was the incidence of severe bleeding (1.38% vs. 1.55%, P=NS). The rates of gastrointestinal hemorrhage and of severe gastrointestinal hemorrhage were significantly lower for clopidogrel than for aspirin, again suggesting reduced gastrotoxicity (gastrointestinal hemorrhage, 1.99% vs. 2.66%; severe gastrointestinal hemorrhage, 0.49% vs. 0.71%; $P<0.05$ for both between-group comparisons).[15]

As noted above, except in selected patients with recent coronary events and/or procedures, the combination of clopidogrel and aspirin is not recommended for the prevention of secondary cerebrovascular events.[2,10] Two studies, Management of Atherothrombosis with Clopidogrel in High Risk Patients (MATCH) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA), evaluated this combination in comparison with clopidogrel monotherapy (MATCH) or with aspirin monotherapy (CHARISMA).[16,17] In MATCH, which enrolled patients with recent (within the previous 3 months) ischemic stroke or TIA, the combination was associated with a nonsignificant 1% reduction in absolute risk for the primary composite outcome (ischemic stroke, myocardial infarction, vascular death, or rehospitalization) versus clopidogrel monotherapy.[16] However, this was more than outweighed by significant increases in life-threatening and major bleeding events. Life-threatening bleeding events were experienced by 96 patients (2.55%) receiving aspirin plus clopidogrel and 49 patients (1.30%) receiving clopidogrel alone; while major bleeding events were experienced by 73 patients (1.94%) and 22 patients (0.58%), respectively. The absolute risk increases for combination therapy versus clopidogrel monotherapy were 1.26% for life-threatening bleeds and 1.36% for major bleeds ($P<0.0001$ for both comparisons).[16] Similar patterns were observed in CHARISMA (in which the comparison was between combination therapy and aspirin alone), which enrolled a broader range of patients with vascular risk factors or symptomatic vascular disease.[17]

Aspirin Plus ER-DP

The efficacy of aspirin plus ER-DP in secondary cerebrovascular event prevention was established in the ESPS-2 study, which used a 2×2 factorial design resulting in four treatment arms: placebo, aspirin 50 mg/day, ER-DP 400 mg/day, and aspirin plus ER-DP.[11] Compared with placebo, the monotherapy arms reduced secondary stroke risk to a similar degree: the 24-month stroke risk was 15.8% for placebo, 12.9% for aspirin alone, and 13.2% for ER-DP alone (odds ratio [OR] vs. placebo: aspirin, 0.79; 95% CI: 0.65-0.97; ER-DP, 0.81; 95% CI: 0.67-0.99). However, the aspirin plus ER-DP formulation demonstrated additive efficacy, reducing the 24-month stroke

risk to 9.9% (OR vs. placebo, 0.69; 95% CI: 0.48-0.73).[11] Moreover, the aspirin plus ER-DP combination was also significantly superior to either of the monotherapy arms with respect to risk reduction for secondary stroke (RRR vs. aspirin, 23.1%, *P*=0.006; vs. ER-DP, 24.7%, *P*=0.002, ARR vs. aspirin, 3% at 2 years, or about 1.5% annually).[11] Both the AHA/ASA and ACCP guidelines consider aspirin plus ER-DP to be an acceptable option for prevention of secondary cerebrovascular events.[2,10]

The ESPIRIT study evaluated the use of aspirin alone versus an aspirin/dipyridamole combination in over 2700 patients with a previous minor cerebrovascular accident or TIA.[18] Although the patients were randomly assigned to different treatment arms, the treatments were not blinded and the nonfixed doses of aspirin were at the discretion of the investigator. Fatal and nonfatal vascular events occurred in 13% of the aspirin/dipyridamole patients and in 16% of the aspirin monotherapy patients (HR, 0.80; 95% CI: 0.66-0.98; absolute risk reduction [ARR], 1% per year; 95% CI: 0.1-1.8). ESPIRIT supports the benefit of the aspirin/dipyridamole combination over aspirin monotherapy.[18]

The 2010 AHA/ASA guidelines consider the evidence supporting aspirin plus ER-DP (level 1, class of evidence B) more compelling than that supporting clopidogrel (level 2b, class of evidence B).[2] Primarily on the basis of ESPS-2, the 2008 ACCP consensus guidelines recommend aspirin plus ER-DP over aspirin alone.[10] It should be noted that the fixed-dose combination of aspirin plus ER-DP is the only prescription antiplatelet agent with an indication for preventive therapy following TIA, as well as following stroke.[19,20]

It is important to note that immediate-release dipyridamole (IR-DP), given separately with aspirin, should not be substituted for the fixed-dose combination of ER-DP plus aspirin. The fixed-dose combination of aspirin plus ER-DP incorporates a tartaric acid core that provides superior dipyridamole dissolution and consistent bioavailability, especially in patients with reduced gastric pH resulting from the use of proton-pump inhibitors.[21]

The safety of aspirin plus ER-DP is generally similar to that of aspirin; the relatively low aspirin dose results in a moderately low rate of bleeding adverse events. In ESPS-2, the incidence of bleeding (at any site) was similar for aspirin monotherapy and aspirin plus ER-DP (8.2% and 8.7%, respectively) and for both placebo and ER-DP monotherapy (4.5% and 4.7%, respectively).[11] In the Prevention Regimen For Effectively Preventing Second Stroke (PRoFESS) study, which compared aspirin plus ER-DP to clopidogrel monotherapy in patients with recent ischemic stroke, there were slightly more major bleeding events in patients receiving aspirin plus ER-DP than in those receiving clopidogrel (4.1% vs. 3.6%; HR 1.15; 95% CI: 1.00-1.32), and more episodes of intracranial bleeding (1.4% vs. 1.0%; HR 1.42; 95% CI: 1.11-1.83).[22] However, the overall incidence of any bleeding event was similar between groups (5.3% vs. 4.9%; HR 1.08; 95% CI: 0.96-1.22).[22]

The most frequent adverse event specific to ER-DP that affects tolerability is headache; in ESPS-2 the incidence of headache was similar for ER-DP monotherapy and aspirin plus ER-DP (37% and 38%, respectively) and for placebo and aspirin monotherapy (32% and 33%, respectively).[11] Headache was also the most frequent reason for treatment discontinuation in clinical studies of aspirin plus ER-DP, reported by 10% of patients receiving the combination or ER-DP monotherapy, compared with 3% for aspirin monotherapy and 4% for placebo.[19] In summary, the addition of ER-DP to aspirin confers little or no incremental bleeding risk and an increase in headache risk.

MANAGEMENT OF SIDE EFFECTS ASSOCIATED WITH ANTIPLATELET THERAPY

Bleeding

Bleeding is by far the most clinically significant adverse event associated with antiplatelet regimens. The clinician should assess the patient for evidence of increased bleeding risk, such as a history of bleeding disorders, gastrointestinal bleeding episodes, and/or ulcers. In clinical trials, the risks of bleeding episodes are classified as severe, moderate, or minor bleeding. Severe bleeding is generally defined as fatal bleeding, intracranial bleeding, or bleeding causing hemodynamic compromise requiring blood or fluid replacement, inotropic support, and/or surgical intervention. Moderate bleeding requires transfusion or fluids but does not qualify as severe bleeding, and minor bleeding is clinically insignificant.[17]

Clinical trial evidence in patients with recent stroke or TIA suggests that the risk for major hemorrhage associated with aspirin monotherapy or aspirin plus ER-DP may be slightly greater than that associated with clopidogrel monotherapy; however, the magnitude of increased risk is small (approximately 1 per 500 patient-years of treatment).[2] In patients with increased bleeding risk, any of these options are acceptable, as the benefits for all continue to strongly outweigh the risks. However, such patients should be instructed on the signs and symptoms of bleeding complications, to ensure that they seek immediate medical assistance in the event of a bleeding episode.[19]

The decision to discontinue antiplatelet therapy prior to surgical procedures should be approached according to both the bleeding risk inherent in the planned surgical procedure (which varies widely depending on the procedure) and the increased vascular risk associated with discontinuation (which may include increased perioperative thrombotic risk).[23,24] Also, there remains considerable debate as to how to balance the potential risk of antiplatelet therapy in patients with increased risk for bleeding disorders, particularly gastrointestinal bleeding. The recent ACCP guidelines recognize this challenge, emphasizing the need to balance the potential protective benefit of antiplatelet therapy against the potential risk of bleeding.[25]

It should be noted that antiplatelet therapy following ischemic stroke or TIA is associated with a slight increase in risk for hemorrhagic stroke; however, this is overwhelmingly outweighed by the substantial reduction in risk for ischemic stroke. In a meta-analysis of antiplatelet therapy studies, the Antiplatelet Trialists found that among patients with previous stroke or TIA, the OR associated with antiplatelet therapy versus controls for hemorrhagic stroke was 1.2, while the OR for ischemic stroke was 0.75. Although the relative magnitude of these ORs is similar, the absolute magnitude of reduced risk for ischemic stroke outweighs that of the increased risk for hemorrhagic stroke, because of the far greater incidence of ischemic stroke; the resulting OR associated with antiplatelet therapy for stroke of any kind is 0.77.[26]

When bleeding does occur in a patient already receiving antiplatelet therapy, there are no clear consensus guidelines as to how to treat the bleeding, and a complete discussion is beyond the scope of this paper. In general, antiplatelet-associated bleeding manifests itself as bleeding from a specific source, usually gastrointestinal and rarely (fortunately) intracranial, and therapy is directed at the traditional management of that bleeding site.[2, 10, 25]

Headache

Headache is an adverse event specific to the dipyridamole component of the aspirin plus ER-DP combination. The incidence of headache is relatively high upon initiation of aspirin plus ER-DP and is most notable during the first month of treatment, but declines thereafter.[19] Data from a study among healthy volunteers strongly suggest that headache associated with aspirin plus ER-DP is a transient phenomenon, and that development of tolerance for the ER-DP component is rapid. The incidence of headache following initiation of aspirin plus ER-DP declined from 67% on the first day of treatment to 3% during days 9-10.[27] Therefore, patients who experience dipyridamole-related headache upon initiation of aspirin plus ER-DP should be advised of the strong likelihood that headaches will rapidly subside; most will be able to "push through" the first 2 weeks of therapy until this occurs.

For patients who find headache intolerable, initiating treatment with a reduced dose of aspirin plus ER-DP has been found to substantially reduce the incidence of dipyridamole-induced headache.[28] Although this study did not address the efficacy of reducing ER-DP dose once treatment has started at a standard dose, the manufacturer of aspirin plus ER-DP recommends that the dose of aspirin plus ER-DP be reduced to a single capsule at bedtime, accompanied by low-dose aspirin in the morning for patients who develop intolerable headache at treatment initiation.[19] Because there are no outcome data for this dosing regimen, patients should return to the normal dosing regimen (one capsule in the morning and at bedtime) as soon as possible (typically within 1 week).[19]

Other Adverse Events

Some patients may be allergic to aspirin or to clopidogrel. In such patients, the alternative agent should be substituted: aspirin plus ER-DP for patients allergic to clopidogrel, and clopidogrel for patients allergic to aspirin. Some patients also experience gastrointestinal intolerability to aspirin, which may or may not be associated with gastrointestinal bleeding. Clopidogrel may be an acceptable alternative for such patients.

Finally, there is some evidence that clopidogrel might slightly increase the risk of thrombotic thrombocytopenia purpura (TTP), a very rare multisystemic disorder with microangiopathic hemolytic anemia, fever, neurologic changes, and renal failure. It is frequently fatal, and idiopathic cases occur in about 3.7 per million patients.[29]

Ticlopidine leads to TTP in about one in 5000 patients. Clopidogrel therapy has been associated with TTP, often after a short course of less than 2 weeks. However, the number of cases that have been investigated is small, and the mechanism of induction of TTP by clopidogrel is not clear.[29]

DISCUSSION

Antiplatelet therapy is universally indicated following an ischemic cerebrovascular event. It cannot be overemphasized that antiplatelet treatment following TIA is just as essential as it is following stroke, as the risk for secondary events is similarly very high after both types of event. Although all recommended antiplatelet regimens are associated with some risk of adverse events, the risk and potential impact of these side effects is negligible compared with the risk and impact of secondary stroke.

The impact of bleeding adverse events can be ameliorated by assessing patients for bleeding

risk prior to initiating antiplatelet therapy, and by instructing them accordingly. Patients at high risk for bleeding events should be specifically advised as to the signs and symptoms of bleeding complications, and instructed to seek emergency care if they occur. Headache associated with aspirin plus ER-DP is nearly always transient, and can be managed by "pushing through" the early days of treatment, or by the temporary use of a reduced-dose regimen.

In conclusion, concern about adverse events associated with antiplatelet therapy for secondary stroke prevention should not dissuade clinicians from prompt initiation of therapy following an ischemic cerebrovascular event, and patients should be regularly assessed for treatment adherence and for the development of side effects that may affect adherence.

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