

# Antiplatelet Therapy for Prevention of Secondary Stroke

# Assessing the Evidence

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## Inside this issue:

- Clinical Implications of Ongoing Trials—PROFESS, ACTIVE, SPS3, CASTIA, FASTER, ARCH
- Unanswered Questions and Unmet Needs in Preventive Therapy
- Role of Aspirin + Clopidogrel for Prevention of Recurrent Stroke

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## STATEMENT OF NEED

Stroke is the most common cause of disability in the United States. Each year, an estimated 500,000 people experience a first stroke, and 200,000 have recurrent strokes. Twenty-two percent of men and 25% of women who have an initial stroke die within 1 year. This percentage is even higher among those 65 and older. The risk of recurrent stroke is approximately 13% during the first year and 4% each year thereafter, making prevention of recurrent stroke an important therapeutic goal.

Antiplatelet therapy is a proven component of secondary stroke prevention in patients with transient ischemic stroke (TIA) or ischemic stroke, the most common type in American adults. Several different therapeutic approaches have been used with drugs of this class. Clopidogrel and ticlopidine act by inhibiting adenosine diphosphate (ADP)-induced platelet aggregation, and both require biotransformation for their pharmacologic activity. Clopidogrel is a specific inhibitor of ADP-mediated platelet aggregation. Its effect on ADP binding is irreversible, and lasts for the duration of platelet life. Aspirin is a nonspecific inhibitor of cyclooxygenase (COX) enzyme, thereby decreasing thromboxane-A<sub>2</sub> (TXA<sub>2</sub>)-mediated platelet aggregation. Combination therapy with dipyridamole plus aspirin may act against platelet aggregation via several possible mechanisms. It directly stimulates prostacyclin synthesis, potentiates the platelet inhibitory actions of prostacyclin, and inhibits phosphodiesterase from raising platelet cyclic AMP (cAMP) levels. The efficacy and safety of antiplatelet therapy are major concerns for healthcare providers and patients, and it is important that the various mechanisms of action and potential risks of use are understood and evaluated.

## TARGET AUDIENCE

This activity is designed for neurologists.

## ACTIVITY GOAL

The goal of this activity is to provide neurologists with medical information, which should aid them in delivering better care to their patients.

## LEARNING OBJECTIVES

Upon completion of this activity, participants should be better able to:

- Review unanswered questions in secondary stroke prevention, which may be addressed by ongoing clinical trials with approved antiplatelet therapies
- Describe several major, ongoing trials of antiplatelet therapy for secondary stroke prevention: PROFESS, ACTIVE, SPS3, CASTIA, FASTER, and ARCH
- Explain the clinical implications of these trials for the preventive therapy of individual patients

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# ISSUE 6: Unanswered Questions in Dual Antiplatelet Therapy: Ongoing Trials

## LEARNING OBJECTIVES

1. Review unanswered questions in secondary stroke prevention, which may be addressed by ongoing clinical trials with approved antiplatelet therapies.
2. Describe several major, ongoing trials of antiplatelet therapy for secondary stroke prevention: PROFESS, ACTIVE, SPS3, CASTIA, FASTER, and ARCH.
3. Explain the clinical implications of these trials for the preventive therapy of individual patients.

## SECONDARY STROKE PREVENTION: UNANSWERED QUESTIONS, UNMET NEEDS

Ischemic stroke remains a major public health problem, with morbidity, mortality, and cost burden reflecting worldwide inadequacy of stroke prevention efforts.<sup>1</sup> Strategies for secondary stroke prevention include control of risk factors such as cholesterol, blood pressure, lifestyle modification, etc, and antiplatelet and anticoagulation therapy. Ongoing research in stroke prevention with antiplatelet drugs is of great urgency. Most recently, the findings from the ESPRIT trial provided further evidence that, for the prevention of secondary stroke, the combination of extended-release (ER) dipyridamole plus aspirin is superior to aspirin alone.<sup>2</sup> Currently, several major studies are evaluating prevention of secondary stroke in patient subgroups treated with various antiplatelet drug regimens. The studies, which are reviewed briefly in this newsletter, help answer several important questions:

1. What is the proper role of dual aspirin + clopidogrel therapy in secondary stroke prevention? This question is exceedingly important in light of recently published results from the MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk

Patients) and CHARISMA (Clopidogrel for High Atherosclerotic Risk and Ischemic Stabilization, Management, and Avoidance ) trials; these results showed that, in secondary stroke prevention, bleeding risk with the combination of aspirin + clopidogrel outweighs any additive efficacy benefit.<sup>3-5</sup>

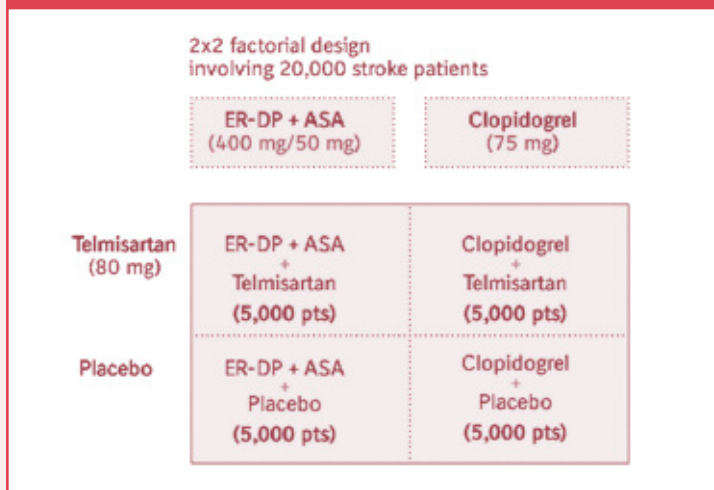
2. Is aspirin + ER dipyridamole more effective than a clopidogrel-based regimen? This is a critical question. As noted in the 2006 American Heart Association (AHA) guidelines for secondary stroke prevention, “insufficient data are available to make evidence-based recommendations with regard to choices between antiplatelet options other than aspirin.”<sup>3</sup>
3. Is the addition of a blood pressure-lowering medication (eg, an angiotensin-receptor blocker [ARB]) to standard stroke prevention therapy of preventive value?<sup>6</sup>
4. What are appropriate preventive strategies in special populations—patients with atrial fibrillation (AF; a major cardioembolic cause of ischemic stroke),<sup>7</sup> small subcortical strokes,<sup>8</sup> aortic arch atheroma,<sup>9</sup> and the acute stage of stroke?<sup>10</sup>

## PROFESS®

PROFESS (Prevention Regimen for Effectively avoiding Second Strokes) is the largest trial to date for secondary stroke prevention.<sup>1</sup> The recruitment window for PROFESS was officially closed on July 16, 2006. Overall, 20,333 patients were randomized from 720 sites in 35 countries.<sup>11</sup> This randomized, parallel-group, multinational, double-blind, double-dummy, active and placebo-controlled trial will utilize a 2x2 factorial design (Figure 1), in which all patients receive either 25 mg aspirin + 200 mg ER dipyridamole or clopidogrel.<sup>11</sup> Originally, the comparator was a combination of aspirin + clopidogrel, but the results of the MATCH trial (see above) prompted investigators to switch to clopidogrel alone to minimize bleeding risk.<sup>12</sup> In addition, half of the total population will also receive the ARB telmisartan (80 mg/day), and half will receive placebo, to determine any additional preventive efficacy from ARB therapy.<sup>13</sup> ARBs are promising agents because data suggest that blockade of angiotensin II, in addition to reducing blood pressure, may provide additional vascular protective benefits favorable for stroke patients.<sup>1,14</sup> Follow-up of PROFESS will last up to 4 years, with a primary outcome of time to second stroke and many secondary vascular outcomes.<sup>1,15</sup> PROFESS

### FIGURE 1

Design of PROFESS<sup>11</sup>



# TABLE 1

Brief Summary of Studies

STUDY	PROJECTED N	POPULATION	DESIGN/COMPARISON	PRIMARY OUTCOME
PROFESS <sup>1,4, 10,11,12,13,15,17</sup>	20,333	Recent ischemic stroke history	Randomized, double-blind, multicenter 2x2 factorial <b>ASA + ER-DP vs C; T</b> in half of population	Time to second stroke
ACTIVE <sup>7,8,10,17</sup>	14,000	AF history with $\geq 1$ risk factor for stroke (including prior stroke/TIA)	All ACTIVE trials are multicenter ACTIVE W (completed): randomized, open, noninferiority trial <b>W vs ASA + C</b> ACTIVE A: double-blind <b>ASA + C vs ASA</b> ACTIVE I: partial factorial, double-blind <b>Irbesartan (I)</b> or placebo added to regimen of ACTIVE W or A	Composite of first occurrence of stroke, non-CNS systematic embolism, MI, vascular death (ACTIVE I eliminates non-CNS systemic embolism and adds hospitalization for heart failure)
SPS3 <sup>24</sup>	2500	Small subcortical stroke history	Factorial, multicenter <b>ASA + C vs ASA</b> ; hypertensive subset receives usual or aggressive BP reduction therapy	Stroke prevention
CASTIA <sup>10,19-22</sup>	2400	Acute ischemic stroke/TIA (first 24 h)	Randomized <b>ASA + C vs ASA</b>	Composite of stroke, new MRI-documented infarction, MI, vascular death
FASTER <sup>20,23</sup>	500 (pilot) 7500 (total)	Acute ischemic stroke/TIA (first 24 h)	Randomized, double-blind, multicenter 2x2 factorial 4 arms of study: <b>ASA alone; ASA + C; ASA + S; ASA + C + S</b>	Recurrent stroke
ARCH <sup>9,17,25</sup>	1500	Atherosclerosis of aortic arch Recent (<6 months) cerebral or peripheral embolic event)	Open, randomized, multicenter <b>W vs ASA + C</b>	Composite of recurrent stroke, acute MI, peripheral embolism, vascular death

ASA = aspirin; ER-DP = extended-release dipyridamole; C = clopidogrel; T = telmisartan; W = warfarin (or, in ACTIVE, the available vitamin K antagonist anticoagulant); I = irbesartan; S = simvastatin

also includes substudies on cognition, MRI evidence of subclinical disease, vascular hemodynamics, and urine and blood chemistry.<sup>13</sup> Researchers expect results in 2008.<sup>12</sup> Hopefully, PROFESS will help to answer the question of the relative efficacy of aspirin + ER dipyridamole versus clopidogrel, and provide evidence on the preventative role of the addition of an ARB.

## ACTIVE

Another important study underway is ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for Vascular Events). This multicenter trial plans to enroll a total of 14,000 patients with AF and at least 1 risk factor for stroke, including but not limited to prior stroke or TIA.<sup>7</sup>

ACTIVE comprises 3 component trials—ACTIVE W, ACTIVE A, and ACTIVE I. ACTIVE W is a randomized, open, noninferiority trial comparing oral anticoagulation therapy (target international normalized ratio [INR] of 2 to 3) with aspirin (75 to 100 mg/day) + clopidogrel (75 mg/day).<sup>7</sup> ACTIVE A, which included patients ineligible for randomization to anticoagulation, is a double-blind comparison of clopidogrel + aspirin with aspirin alone.<sup>7</sup> Patients participating in ACTIVE W or A could be enrolled in ACTIVE I, a partial factorial, double-blind trial in which irbesartan (300 mg/day) or placebo is added to the regimen of ACTIVE W or A.<sup>7</sup> Planned follow-up is 3 years (mean).<sup>7</sup> For

ACTIVE W and A, the primary outcome is the composite of first occurrence of stroke, non-central nervous system (non-CNS) systemic embolism, myocardial infarction (MI), or vascular death, with major bleeding as a secondary outcome.<sup>7</sup> ACTIVE I has 2-part primary outcomes of stroke, MI, and vascular death with and without hospitalization for heart failure.<sup>7</sup>

Although ACTIVE A and I remain ongoing,<sup>16</sup> ACTIVE W was recently terminated prematurely because of “clear evidence of superiority of anticoagulation therapy” compared with aspirin + clopidogrel.<sup>16</sup> Oral anticoagulation provided more effective prevention of the primary endpoint events ( $P = .0003$ ) and of stroke ( $P = .001$ ; Figure 2).<sup>16</sup> Minor bleeding was more common with aspirin + clopidogrel ( $P = .0009$ ), with major bleeding similar between the groups; total incidence of hemorrhage was significantly greater with aspirin + clopidogrel than with anticoagulation.<sup>16</sup>

## SPS3

Small subcortical strokes (S3), also known as lacunar or small-vessel strokes, account for about 25% of brain infarctions and are associated with vascular dementia. These strokes are especially frequent in younger and minority populations, and patients with symptomatic S3 strokes have a recurrent stroke rate of 8%.<sup>8</sup> Secondary Prevention of Small Subcortical

Strokes (SPS3) is a 45-center, randomized trial that will assess stroke prevention (primary endpoint) and cognition (secondary endpoint) in a planned cohort of 2500 patients with a history of S3.<sup>8,10,17</sup> A factorial design will compare aspirin + placebo vs aspirin + clopidogrel; hypertensive patients in these 2 groups will also receive either usual blood pressure control (to a target of 130-149 mmHg systolic BP) or intensive control (to a target of <130 mmHg systolic BP).<sup>8</sup> Mean follow-up will be 3 years.<sup>8</sup> SPS3 will provide data on the stroke prevention with aspirin + clopidogrel in a population with cerebrovascular manifestations of atherothrombosis.<sup>18</sup>

## CASTIA

Can acute antiplatelet treatment make a difference in stroke recurrence? Clopidogrel in Acute Stroke and TIA (CASTIA) will randomize a projected 2400 patients with acute, minor ischemic stroke or TIA within the first 24 hours of symptom onset; all patients will be treated with aspirin, 75 mg/day, and will also receive either placebo or clopidogrel at an initial loading dose of 300 mg/day followed by maintenance at 75 mg/day.<sup>10,19,20</sup> Primary composite outcome will include stroke, new infarction documented by MRI, MI, and vascular death at 90 days of follow-up.<sup>19,20</sup>

## FASTER

The preventive benefits of acute care are also the subject of FASTER (Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence).<sup>21,22</sup> This randomized, double-blind trial is expected to enroll 500 stroke/TIA patients at 19 centers

in a pilot phase, eventually enrolling 7500 patients if the pilot proves feasibility.<sup>19-23</sup> FASTER will use a 2x2 factorial design: in the first 24 hours after stroke/TIA, all patients will be treated with aspirin, and randomized to placebo or clopidogrel (300 mg/day load, followed by 75 mg/day) and to placebo or simvastatin 40 mg/day.<sup>19-22</sup> This creates 4 possible treatment arms: aspirin alone, aspirin + clopidogrel, aspirin + simvastatin, and aspirin + clopidogrel + simvastatin.<sup>23</sup> Eligible patients will not be candidates for acute thrombolytic therapy.<sup>21,22</sup> Patients will be treated for 1 month, and follow-up will be 90 days.<sup>19-22</sup> The primary outcome measure is recurrent stroke.<sup>19,20</sup> Results of FASTER's pilot program are anticipated soon,<sup>19,20</sup> and will provide some indication of the utility of dual antiplatelet therapy, with or without a statin for short-term stroke prevention.

## ARCH

Aortic arch atheroma is a significant risk factor for ischemic stroke.<sup>9</sup> To date, there has been no evidence regarding the choice of preventive strategies for recurrent stroke in this population.<sup>9</sup> ARCH (Aortic Arch Related Cerebral Hazard) is an open, randomized trial with a projected enrollment of 1500 patients at 15 centers, enrolling patients with atherosclerosis of the aortic arch and a recent (less than 6 months) cerebral or peripheral embolic event.<sup>9,17</sup> The study will compare oral anticoagulation with warfarin (target INR, 2-3) vs aspirin 75 to 325 mg/day + clopidogrel 75 mg/day.<sup>9</sup> The primary outcome is a composite of recurrent stroke, acute MI, peripheral embolism, or vascular death.<sup>9</sup> ARCH will be the first trial to



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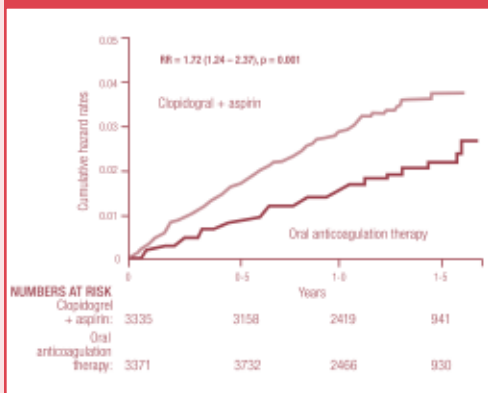


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## FIGURE 2

Risk of stroke, ACTIVE W<sup>7</sup>



assess prevention of secondary stroke in this subpopulation.<sup>9</sup>

### SUMMATION

For ease of review, all 6 studies presented above are summarized in Table 1.

### CLINICAL IMPLICATIONS

PRoFESS will help determine whether aspirin + ER dipyridamole is superior to clopidogrel therapy in the prevention of recurrent stroke. PRoFESS, along with ACTIVE I, will also enhance our understanding of ARB-based therapy in stroke prevention. All the ACTIVE trials will provide data on the value of combination therapy with aspirin + clopidogrel for secondary prevention in patients with AF; ACTIVE W, however, has already shown that oral anticoagulation remains a superior choice to aspirin + clopidogrel. The results warrant no change

in current AHA recommendations for secondary stroke prevention in the context of AF—oral anticoagulation with warfarin to an INR of 2 to 3, with aspirin 325 mg/day reserved as an alternative only for patients who cannot take anticoagulants.<sup>3</sup> SPS3 and ARCH will gather important data on prevention in 2 key subgroups with significant stroke morbidity—patients with lacunar stroke and patients with atherosclerosis of the aortic arch. CASTIA and FASTER may show whether acute dual antiplatelet therapy, given in the first 24 hours of stroke/TIA, can prevent stroke recurrence in the short term; FASTER will also assess the contribution of blood pressure and lipid control in short-term stroke prevention. Thus, data from ongoing trials will move us closer to an important goal—increasingly tailored therapy for ischemic stroke based on patient profile and characteristics of stroke.<sup>3</sup>

### SUMMARY

- Ischemic stroke remains a major public health problem, so ongoing research in stroke prevention is of great urgency.
- Several major studies are currently evaluating prevention of secondary stroke; the studies will answer important clinical questions regarding:
  - The proper role of aspirin + clopidogrel therapy
  - Comparative efficacy of aspirin + ER dipyridamole vs clopidogrel
  - Preventive value of blood-pressure reduction, particularly with ARBs, which may have favorable vascular effects in addition to antihypertensive effects

### Unanswered Questions in Dual Antiplatelet Therapy: Ongoing Trials

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#### POSTTEST

- a.  b.  c.  d.
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#### EVALUATION

- |     | Poor                     | Satisfactory             | Good                     | Very Good                | Excellent                |
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If you would like to receive future educational programs on the topic of **neurology**, please check this box:

- Preventive strategies for special stroke populations
- PROFESS will be the largest trial to date for secondary stroke prevention and will compare aspirin + ER dipyridamole vs clopidogrel with and without the ARB, telmisartan
- In patients with AF and  $\geq 1$  stroke risk factor, ACTIVE A and ACTIVE I will assess aspirin alone vs aspirin + clopidogrel, with and without the ARB, irbesartan
  - ACTIVE W, already complete, was stopped early because it showed clear superiority of oral anticoagulation over aspirin + clopidogrel
- SPS3 will evaluate aspirin alone versus aspirin + clopidogrel, with usual or

- aggressive blood pressure control, in patients with a history of small subcortical stroke
- CASTIA compares aspirin alone vs aspirin + clopidogrel in acute stroke and TIA to prevent early stroke recurrence
- FASTER will also study aspirin with and without clopidogrel in acute stroke/TIA along with the effects of lipid lowering with simvastatin
- Prevention in patients with atherosclerosis of the aortic arch will be evaluated in ARCH, which compares oral anticoagulation with aspirin + clopidogrel
- Data from these trials will enable the increasing individualization of secondary stroke prevention

## EVALUATION

1. How well did the activity meet the identified Statement of Need?
2. How would you rate your satisfaction with this activity?
3. How well did this activity help you meet the following objectives:
  - a. Review unanswered questions in secondary stroke prevention, which may be addressed by ongoing clinical trials with approved antiplatelet therapies
  - b. Describe several major, ongoing trials of antiplatelet therapy for secondary stroke prevention: PROFESS, ACTIVE, SPS3, CASTIA, FASTER, and ARCH
  - c. Explain the clinical implications of these trials for the preventive therapy of individual patients
  - d. Evaluate whether the activity was free from commercial bias.
4. Assess the degree to which this activity is helpful in your practice.
5. How would you rate the objectivity, balance, and scientific rigor of this activity?
6. How does this activity rate in comparison to other activities you have participated in?

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## Unanswered Questions in Dual Antiplatelet Therapy: Ongoing Trials

### Posttest

1. Why are ongoing trials in secondary stroke prevention so urgently needed?
  - a. No evidence is currently available on secondary prevention.
  - b. Ischemic stroke is a major public health problem.
  - c. Clinicians seek one preventive strategy to cover all patient types.
  - d. All of the above.
2. Which of the following is NOT a question that will be addressed by ongoing trials in secondary stroke prevention?
  - a. What is the role of combination therapy with aspirin + clopidogrel?
  - b. Is aspirin + ER dipyridamole more effective than a clopidogrel-based regimen in prevention of recurrent stroke?
  - c. Is lipid reduction more effective than antiplatelet therapy for secondary prevention?
  - d. Is the addition of an ARB of preventive value?
3. True or false: PROFESS will help answer the question of the relative efficacy of aspirin + ER dipyridamole versus clopidogrel.
  - a. True
  - b. False
4. In PROFESS and ACTIVE I, why are the ARBs telmisartan and irbesartan being studied?
  - a. They minimize adverse events of antiplatelet therapy.
  - b. They reduced the risk of heart failure.
  - c. They may offer additional vascular protective benefits in addition to blood pressure reduction.
  - d. They provide faster reductions in blood pressure than other antihypertensive drugs.
5. Why was ACTIVE W terminated early?
  - a. There was no evidence of preventive efficacy with oral anticoagulation in AF patients.
  - b. There was evidence of superiority of oral anticoagulation versus aspirin + clopidogrel in AF patients.
  - c. Results were inconclusive.
  - d. Bleeding risk was too high with all treatments.
6. True or false: SPS3 will compare aspirin alone with aspirin + simvastatin in lacunar stroke patients.
  - a. True
  - b. False
7. Which study will evaluate antiplatelet therapy in acute stroke/TIA for the prevention of early recurrence?
  - a. CASTIA
  - b. FASTER
  - c. ARCH
  - d. a and b only
8. The primary outcome studied for the PROFESS study can be best described as:
  - a. A composite outcome including stroke new infarction documented by MRI and vascular death.
  - b. The largest trial to date for secondary stroke prevention.
  - c. A study of the utility of treatment of hyperlipidemia and antiplatelet therapy in stroke prevention.
  - d. All of the above.
9. Complete the sentence: The ARCH trial...
  - a. Will be the first to assess secondary stroke prevention in patients with aortic arch atheroma.
  - b. Will compare oral anticoagulation to aspirin + clopidogrel.
  - c. Will enroll 1500 patients with atherothrombosis of the aortic arch, and a recent (less than 6 months) cerebral or peripheral embolic event
  - d. All of the above.
10. Which of the following is an important clinical implication of the ongoing trials?
  - a. The trials will increase our ability to tailor stroke preventive strategies.
  - b. The trials will codify one preventive strategy that works in most patients.
  - c. The trials will show whether control of two risk factors, blood pressure and lipids, is more effective than antiplatelet or anticoagulant therapy for secondary prevention.
  - d. All of the above.

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