UPDATE ON ANTITHROMBOTIC AGENTS IN SECONDARY STROKE PREVENTION

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SUMMARY –Recurrent stroke is a major cause of morbidity and mortality among stroke survivors. With improved survival after first ischemic stroke, stroke recurrence may account for a greater share of the future annual cost of stroke-related health care. Despite advances in stroke prevention strategies and treatments, stroke recurrence is still the major threat to any stroke survivor. This review discusses antithrombotic therapy in secondary stroke prevention which has a major impact in clinical practice.

Key words: *Stroke - prevention and control; Secondary prevention; Platelet aggregation inhibitors - therapeutic use; Anticoagulants*

Introduction

Stroke is the third leading cause of death and the main cause of disability in the United States[1]. About 15% to 26% of all strokes are preceded by a transient ischemic attack (TIA)[2], and the risk of stroke after TIA or minor stroke is 8.4%[3] to 10% at 3 months[4]. Although traditionally a distinction has been made between TIA and stroke, magnetic resonance imaging data have shown that many individuals with TIA, particularly after prolonged events, have imaging evidence of cerebral infarction[5]. Therefore, the approach to secondary prevention after stroke or TIA is similar. This brief review mentions recent studies using antithrombotic therapy that impact clinical practice. It is not meant to provide an exhaustive review of current recommendations for secondary ischemic stroke prevention because these have been delineated in recent guidelines[6-8].

Antithrombotic agents in stroke prevention include anticoagulants and antiplatelet agents. Antiplatelet agents are reserved for patients with non-cardioembolic stroke, such as large- or small-vessel-related strokes. Recent studies have contributed to the extensive literature on the role of antithrombotic therapy in secondary stroke prevention. Anticoagulants are prescribed for cardioembolic strokes, venous strokes, and strokes such as related to dissection.

Non-Cardioembolic Strokes

The antiplatelet agents, aspirin (50-325 mg/day), aspirin plus extended release dipyridamole, and clopidogrel monotherapy, are all acceptable options in secondary prevention of strokes of arterial origin[9]. A recent update to existing recommendations states that the combination of aspirin and extended-release dipyridamole is recommended over aspirin alone, and that clopidogrel may be considered over aspirin alone[8].

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Studies that support the use of these agents have been extensively reviewed[6-8]. Other individual antiplatelet agents have been evaluated or are in testing. Triflusal, a compound structurally related to aspirin, was found to have a similar effect as aspirin on the combined end point of stroke, myocardial infarction, and vascular death, but with less hemorrhagic complications; however, it is not available in the United States[10,11]. A novel thienopyridine, prasugrel, has been studied in patients with acute coronary syndromes; when compared with clopidogrel, it resulted in a reduction in myocardial infarction, stroke, and cardiovascular death, at the expense of a slight increase in hemorrhagic risk[12]. Other agents such as thrombin receptor antagonists are being tested; in the current TRA2P-TIMI 50 trial (http://clinicaltrials.gov), one such agent is being tested in addition to standard antiplatelet agents in prevention of coronary and cerebrovascular outcomes.

Given the limited effects of single antiplatelet agents, there has been an interest in combination therapy. The ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) study[13], which was published after the 2006 American Heart Association recommendations, compared aspirin plus extended release dipyridamole and aspirin alone and found an hazard ratio (HR) of 0.8 (95% CI, 0.66-0.98) for the combined end point of stroke, myocardial infarction, vascular death, and major hemorrhage for the combination; the HR for stroke alone was 0.84 (95% CI, 0.67-1.17). This study was limited by the open treatment assignment (although outcome evaluation was blinded), the nonstandard aspirin dose, and discrepancy between the intention-to-treat and on-treatment analysis. Nonetheless, these results validate the findings of the European Stroke Prevention Study 2[14]. Direct comparison of clopidogrel *versus* aspirin plus extended-release dipyridamole in the PRoFESS study has recently demonstrated that the risks of recurrent stroke or the composite of stroke, myocardial infarction, or vascular death are similar with both regimens [15]. However, increased risks of nonfatal hemorrhagic stroke and side effects leading to discontinuation of therapy were significantly often seen with aspirin plus extended-release dipyridamole.

The combination of aspirin and clopidogrel has been utilized in the coronary arteries successfully. Nonetheless, in stroke prevention, this combination has not shown greater efficacy than clopidogrel alone and resulted in greater hemorrhagic risk[16]. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) study[17] evaluated patients with cerebrovascular disease, coronary disease, peripheral vascular disease, or multiple vascular risk factors, who were randomized to receive aspirin or aspirin plus clopidogrel. There was no statistically significant reduction in the primary combined end point of stroke, myocardial infarction, and vascular death (relative risk, 0.93; 95% CI, 0.83-1.05), or of nonfatal ischemic stroke (relative risk, 0.81; 95% CI, 0.64-1.02). Combination therapy resulted in a greater incidence of bleeding than with aspirin alone (severe bleeding: 1.7% combination, 1.3% aspirin; $P = 0.09$; moderate bleeding: 2.1% combination, 1.3% aspirin; $P < 0.001$). These data reinforce prior experience showing lack of efficacy of the combination of aspirin and clopidogrel for secondary stroke prevention[16]. At this point, evidence suggests that the combination of aspirin and clopidogrel is not superior to either agent alone in secondary stroke prevention and results in a greater frequency of hemorrhages. Ongoing studies will further contribute to the understanding of the role of combination aspirin and clopidogrel in stroke reduction. The SPS3 study is currently evaluating aspirin 325 mg plus clopidogrel 75 *versus* aspirin 325 mg alone in preventing stroke recurrence in patients with small subcortical infarcts[18]. The ARCH (Aortic Arch Related Cerebral Hazard) study (http://clinicaltrials.gov) is comparing the combination of aspirin and clopidogrel *versus* warfarin in preventing stroke and systemic embolism in patients with aortoembolic stroke.

Because the risk of stroke after an initial cerebrovascular ischemic event is greatest in the first few days and weeks, particularly with large-vessel disease[19], it is worthwhile to discuss early and acute prophylaxis with antithrombotic agents. Although this should be individualized according to the mechanism of the event, studies have provided important guidelines. Earlier studies[20,21] showed a small benefit of early initiation of aspirin. The combination of aspirin and clopidogrel reduced the presence of microembolic signals in those with recently symptomatic carotid stenosis[22]. Recently, the FASTER trial[4] randomized

patients within 24 hours of their ischemic event to aspirin or aspirin plus clopidogrel. This small study was stopped early and found a nonstatistically significant reduction in the 90-day risk of stroke for combination antiplatelet therapy. Therefore, the use of combination antithrombotic agents in the acute period for a limited time should be further explored in randomized trials, but as yet, there is no definite indication to modify existent recommendations.

Intracranial Stenosis

The WASID study[24] evaluated patients with a recent stroke or TIA caused by intracranial arterial disease of 50% to 99% and randomized participants to aspirin 1,300 mg/day *versus* warfarin international normalized ratio 2 to 3. The study was terminated because of a safety concern. There was no difference in the primary outcome of ischemic stroke, intracerebral hemorrhage, or vascular death between the two treatment arms, which occurred at a staggering 22% during the 1.8-year average follow-up period. Most of the events occurred in the first couple of weeks. However, there was a greater than twofold incidence of major hemorrhage or death in the anticoagulated group. There was no subgroup of patients in whom warfarin was superior to aspirin[24]. Consequently, warfarin appears to be no more effective and riskier than aspirin for this disease. This study also allowed the identification of a group at a high risk of recurrent stroke in the territory of the stenotic vessel, including those with a severe stenosis (70%-99%), women, and enrolment soon after the onset of symptoms[25]. Therefore, an individual presenting with a stroke caused by a 70% to 99% intracranial stenosis would have a 2-year risk of recurrent stroke of 25%, whereas a lower degree of stenosis of 50% to 69% would carry only an 11% risk[25].

Given the increased risk of recurrence, there has been considerable interest in endovascular approaches to intracranial stenosis. Initial experience with balloon-expandable stents was associated with a high risk of periprocedural complications[26], but the development of self-deployed stents appears to provide a safer alternative[27]. The efficacy of endovascular therapy against best medical therapy will be studied in an upcoming study; the SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Stroke in Intracranial Stenosis) study (http://clinicaltrials.gov) will evaluate best medical therapy, including antiplatelet therapy, aggressive LDL reduction, and tight blood pressure control, *versus* endovascular therapy with self-deployed stents in patients with a recently symptomatic intracranial stenosis of 70% to 99%. However, currently, the author believe that intracranial stenting outside a clinical trial should be reserved for those high risk patients who have had recurrent events on medical therapy.

Cardioembolic Stroke

Atrial fibrillation (AF) remains a prominent cause of ischemic stroke worldwide. The incidence of AF increases with age and prevalence reaches 10% in octogenarians[28]. The proportion of strokes attributable to this common arrhythmia will continue to rise as our population ages. In the Framingham Study, almost one fourth of all strokes that occurred in patients aged >80 years were attributable to AF[29]. Given our aging population, it is estimated that by the year 2050, there may be as many as 10 million individuals with atrial fibrillation in this country[30]. Many studies have confirmed the superiority of anticoagulants over placebo and antiplatelet agents in atrial fibrillation. A recent meta-analysis of more than 28,000 subjects[31] concluded that warfarin reduced the relative risk of stroke by 64% (95% CI, 49-74%) compared with placebo, whereas antiplatelet agents reduced the risk by 22% (6%-35%). Direct comparison of anticoagulants *versus* antiplatelet agent showed a 39% (22%-52%) relative risk reduction in favor of warfarin. The risk of intracranial hemorrhage with warfarin compared with aspirin was small, with an absolute increase of 0.2% *per* year. Therefore, current guidelines recommend adjusted dose warfarin (target international normalized ratio, 2.5; range, 2-3) for stroke prevention in AF[6,7].

Nonetheless, the use of warfarin is burdensome because its bioeffects are variable and there is the need for frequent blood testing. This has led to a growing interest in direct thrombin inhibitors, which offer stable dosing, few interactions with other medications, no dietary restrictions, and no need for international normalized ratio testing. Ximelagatran was evaluated in recent studies[32] and found to be as effective as warfarin in preventing recurrent strokes (2.83%/ year with ximelagatran and 3.27%/year with

warfarin; $P = 0.625$), with similar rates for hemorrhagic complications. However, 6% of those treated with ximelagatran had a significant increase in liver enzymes; therefore, this agent was not approved by the FDA for secondary stroke prevention. Another direct thrombin inhibitor, dabigatran, has currently been tested in Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial[33]. Results of RE-LY indicate that warfarin's supremacy for stroke prevention in AF is in jeopardy. RE-LY is the largest stroke prevention trial in patients with AF ever undertaken; over 18 000 patients with AF and at least 1 additional vascular risk factor were randomized to receive 1 or 2 doses of dabigatran or dose-adjusted warfarin. Like ximelagatran, dabigatran etexilate (a prodrug of the active moiety dabigatran) is another direct thrombin inhibitor. Dabigatran is already approved in Europe and Canada for the prevention of venous thromboembolism after hip and knee replacement surgery. Because dabigatran leads to a predictable level of anticoagulation with a low potential for drug-drug or food interactions, blood monitoring is unnecessary. There is an interaction with amiodarone, however, an important consideration in the AF population.

Another common cause of cardioembolism is cardiac failure and reduced ejection fraction. However, little research has been done in antithrombotic therapy of this population. The ongoing WARCEF (Warfarin-Aspirin Reduced Cardiac Ejection Fraction) study is evaluating the effects of aspirin *versus* warfarin in patients with reduced ejection fraction (<35%) in preventing stroke and death[34].

Conclusion

The role of antithrombotic agents in secondary stroke prevention is of major significance. New direct and indirect thrombin inhibitors show great promise in prevention of subsequent stroke. There are still many unanswered questions that will be addressed by ongoing randomized trials that are likely to change the future practice to reduce stroke recurrence.

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Sažetak

ANTIBIOTSKI LIJEKOVI U SEKUNDARNOJ PREVENCIJI MOŽDANOG UDARA

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Ponavljajući moždani udar je najčešći uzrok pobola i smrtnosti među preživjelima nakon moždanog udara. Uz veće preživljavanje nakon prvog ishemijskog moždanog udara, ponavljajući moždani udari zauzimaju velik dio nadolazećih godišnjih izdataka vezanih za zbrinjavanje moždanog udara. Usprkos napretku strategija za prevenciju i liječenje moždanog udara ponovni moždani udar je najopasnija prijetnja bilo kome tko je preživio moždani udar. Ovaj pregledni članak posvećen je antitrombotskoj terapiji u sekundarnoj prevenciji moždanog udara, gdje ima najznačajniji utjecaj u kliničkoj praksi.

Ključne riječi: *Moždani udar, sekundarna prevencija; Trombociti, agregacija, inhibitori – terapijska primjena; Antikoagulansi*