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Window for TPA Administration Expands by Julia Rhodes

Eighty-eight percent of all strokes are classified as ischemic strokes, and are due to either local thrombus formation or to emboli that occlude a cerebral artery.¹ Cerebral atherosclerosis is the causative factor in about 70% of all ischemic strokes. The final result from thrombus or emboli formation is arterial occlusion, decreasing cerebral blood flow and causing ischemia and ultimately infarction distal to the occlusion. There are many risk factors for developing a stroke. Nonmodifiable risk factors include: age, male gender, race (African American, Asian, Hispanic), family history of stroke, and low birth weight. Modifiable risk factors include hypertension and cardiac disease, especially atrial fibrillation, diabetes mellitus, dyslipidemia, and cigarette smoking.¹

The treatment of choice for ischemic stroke is thrombolytic therapy with r-TPA (alteplase), unless there is a contraindication.² Contraindications for r-TPA therapy include any conditions of risk for intracranial or other significant bleeding, recent use of heparin or warfarin, active internal bleeding, recent major surgery or serious trauma, and recent myocardial infarction. r-TPA therapy is currently approved for treatment of ischemic stroke within three hours of onset of symptoms of stroke according to the guidelines for management of acute ischemic stroke published by the American Heart Association/American Stroke Association (AHA/ASA).³ The goals of therapy for acute ischemic stroke are to reduce the ongoing neurologic injury and decrease mortality and long-term disability, as well as to prevent complications secondary to immobility and neurologic dysfunction, and to prevent stroke recurrence.¹

r-TPA works by initiating local fibrinolysis by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin.² The typical therapeutic regimen for r-TPA 0.9 mg/kg/dose, with a maximum of 90 mg. r-TPA should be administered as a bolus dose over 1 minute with 10% of the total patient dose, followed by a continuous infusion over 60 minutes with the remaining 90% of the total dose.³ The most significant adverse effect associated with r-TPA therapy is intracranial hemorrhage.⁴ Aspirin 160 to 325 mg is the current alternative for managing an acute ischemic stroke in patients not receiving thrombolytic therapy.²

European Cooperative Acute Stroke Study III (ECASS III) was a randomized, double-blind, placebo controlled trial, conducted by European investigators to assess the safety and efficacy of administering r-TPA therapy for acute ischemic stroke up to 4.5 hours after onset of symptoms. In this trial, 821 patients were randomly assigned into either the r-TPA or placebo group. r-TPA was administered on average within 3 hours and 59 minutes from onset of stroke symptoms. 52.4% of patients in the r-TPA group showed a statistically significant favorable outcome (defined as Rankin score of 0 or 1) versus 45.2% of patients in the placebo group (p=0.04). Safety endpoints of intracranial hemorrhage and symptomatic intracranial hemorrhage were found to be statistically significant. 27.0% of r-TPA patients experienced intracranial hemorrhage effect versus 17.6% of patients in the placebo group (p=0.001). 2.4% of r-TPA patients versus 0.3% placebo patients suffered a symptomatic intracranial hemorrhage (p=0.008). Investigators found that mortality did not differ significantly among the r-TPA group and the placebo group.⁴ The results of the study suggest that 14 patients needed to be treated with r-TPA therapy within 4.5 hours after onset of stroke symptoms for 1 additional patient to achieve a favorable outcome., and that 45 patients needed to be treated for 1 additional patient to experience a symptomatic intracranial hemorrhage.

Due to the statistically significant benefit of administering r-TPA therapy within 4.5 hours after onset of stroke symptoms demonstrated by the ECASS III trial, the AHA/ASA has expanded the treatment window for use of r-TPA to be up to 4.5 hours after onset of symptoms. This expands the previous guidelines published in 2007, which had established a window of 3 hours after the onset of stroke symptoms. All patients receiving anticoagulant therapy are excluded from the new expanded window of therapy regardless of their international normalized ratio (INR). The new guidelines are set to be published in *Stroke*, a journal published by the AHA/ASA, August 2009.

References

1. Wells BG, DiPiro JT, Schwinghammer TL, DiPiro CV. *Pharmacotherapy Handbook*. 7th ed. McGraw-Hill Companies, Inc; 2009: 156-160.
2. Wijdicks E, Misulis K, Ferri F. *MD Consult*. Elsevier Inc; 2009. Available at: http://www.mdconsult.com/das/pdxmd/body/143544209-3/852663770?type=med&eid=9-u1.0-1_mt_1014487. Accessed June 15, 2009.
3. del Zoppo GJ, Saver JL, Jauch EC, Adams HP. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. *Stroke*. 2009; 40; 1-4.
4. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008; 359: 1317-

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Does Adding Clopidogrel to Aspirin in Atrial Fibrillation Patients Reduce the Incidence of Vascular Events?

By Trevor Hmielewski

Atrial fibrillation has been shown to increase the risk of stroke five-fold.¹ Warfarin has long been the drug of choice for stroke prevention in patients with atrial fibrillation, reducing the risk of stroke in these patients by 64%.¹ However, the incidence of hemorrhage in patients on warfarin therapy is relatively high; the risk of bleeding is 70% higher when compared to aspirin therapy.² Therefore, aspirin is commonly used in patients at a high risk of bleeding, but has only been shown to decrease the risk of stroke by 22%.² Other options are being considered for the prevention of vascular events in high risk patients. Clopidogrel (Plavix®), in conjunction with aspirin, has been proposed as an alternative option in stroke prevention in high risk patients.

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) study looked at the effects of clopidogrel plus aspirin for the prevention of stroke and other vascular events in patients with atrial fibrillation. The study was a randomized, double-blind, multicenter trial with 7554 patients in 33 countries. A total of 832 patients received aspirin plus clopidogrel, while 924 participants were given aspirin plus placebo. The primary outcome was the occurrence of any major vascular event (stroke, myocardial infarction, non-central nervous system embolism, or death). Patients were followed for a median duration of 3.6 years.¹

The results of the primary outcome reported that 22.1% of patients receiving clopidogrel experienced a major vascular event, compared to 24.4% of patients receiving placebo. This led to a relative risk reduction of 9.5% (CI=0.81-0.98, p=0.01, NNT=43.5). Stroke incidence was a secondary outcome, and accounted for most of the reduction in vascular events for patients receiving clopidogrel. Stroke occurred in 7.8% of patients receiving clopidogrel compared to 10.8% of patients receiving placebo, a relative risk reduction of 28% (CI=0.62-0.83, p<0.001, NNT=33.3). A meta-analysis comparing warfarin to aspirin therapy, in contrast, found a stroke reduction rate of 38% for those receiving warfarin.²

The advantage of clopidogrel as opposed to warfarin for anticoagulation lies in the decreased incidence of bleeding. Warfarin was found to increase the risk of major extracranial hemorrhage by 70% and intracranial hemorrhage by 128% when compared to aspirin.² In comparison, in the ACTIVE A trial clopidogrel was shown to increase the risk of major extracranial hemorrhage by 51% and intracranial hemorrhage by 87% compared to aspirin alone.¹ Based upon these study results, patients who are considered to be at a higher risk for bleeding may benefit from clopidogrel therapy plus aspirin, as opposed to warfarin. Since the reduction in stroke is less than the risk of bleeding with warfarin, a risk-benefit analysis should be performed for each patient based upon their individual risk of stroke and bleeding.

References

1. The ACTIVE investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *New Engl Joun Med.* 2009;360:2066-78.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857-67.

Prevention of Non-Vertebral Fractures with Oral Vitamin D

By Tuan Tran

Fractures can lead to increased morbidity and mortality, especially in the elderly population. In recent years, there has been great interest in the role of vitamin D in the prevention of fractures but there has been conflicting information on the antifracture efficacy of vitamin D. There are as many studies showing its efficacy in the prevention of fractures as there are studies disproving its efficacy. Therefore, patients and healthcare professionals are left without a clear, definitive understanding about the role vitamin D may serve.

A recently published meta-analysis in *Archives of Internal Medicine* may offer some new insights in the less explored medical area of using vitamins as pharmacotherapeutic agents. The study identified 137 potentially relevant randomized controlled trials, but included only the 12 trials that met inclusion and exclusion criteria in the primary analysis. The pooled number of participants in this study was 42,279. The primary focus of this study was to determine the efficacy of vitamin D in the prevention of nonvertebral fractures.

The results of this study showed a 14% reduction in the risk of nonvertebral fractures with vitamin D at any dose. When results in the treatment arm were stratified, there was no difference in the incidence of nonvertebral fractures between those who received the lower dose of vitamin D (340-380 IU/day) and those who received placebo (RR=1.02, 95% CI, 0.92-1.15). However, the risk of nonvertebral fractures decreased by a statistically significant 20% in those who received the higher dose of vitamin D (482-770 IU/day) (RR=0.80, 95% CI, 0.72-0.89). This suggests that there may be a dose-dependent effect, and that daily doses of at least 482 IU of vitamin D should be used. The NNT in the higher dose group was 93 (95% CI, 66-160). This means that 93 patients need to be treated with a higher dose of vitamin D to prevent one nonvertebral fracture.



Another pertinent finding from this study was that using vitamin D (cholecalciferol) was associated with a 23% reduction in nonvertebral fractures, compared to a 10% reduction for those who received vitamin D2 (ergocalciferol).

This study reinforces the need for patients 65 years or older to take vitamin D with doses of greater than 400 IU daily. Other literature has suggested doses of at least 800 IU per day be used to prevent fractures, but potential benefit of using high doses of vitamin D may outweigh the risks from toxicity. Vitamin D toxicity is rare, and doses as high as 10,000 IU per day have been used.

References

1. Bischoff-Ferrari H, Willet WC, et al. Prevention of Nonvertebral Fractures With Oral Vitamin D and Dose Dependency. *Arch Intern Med.* 2009; 169(6): 551-561.
2. Vitamin D dosing. *Pharmacist's Letter/Prescriber's Letter* 2009;25(5):250508.

Rosuvastatin and Prevention of Venous Thromboembolism

By Ann Foede

Currently, the recommended medications for the prevention of VTE are unfractionated heparin, low molecular weight heparins and fondaparinux, but a recent study by Glynn et al has shown that rosuvastatin may play a part in helping to prevent VTE.^{1,2}

Rosuvastatin's main mechanism of action is to inhibit cholesterol synthesis.³ It is used to treat high total cholesterol and high low density lipoprotein (LDL) cholesterol to help prevent cardiovascular events (CVEs), such as heart attack or stroke.⁴ This medication (as well as the rest of the statins), also has other effects in the circulation that may help prevent CVEs.⁵ It has been shown to lower C-reactive protein (CRP), an inflammatory protein in the blood that has been associated with CVEs.^{2,6,7} Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) looked to see if rosuvastatin could not only help prevent CVEs, but VTE as well.^{2,8}

The study included 17,802 people: men over the age of 50 and women over the age of 60.^{2,6,8} These were relatively healthy individuals with LDL levels under 130 mg/dL and an average CRP level of 5 mg/L.^{2,6,8} Exclusion criteria included a history of cancer in the previous five years (except basal cell or squamous cell skin cancer), history of chronic inflammatory disease, and use of a medication to lower cholesterol in the six weeks leading up to screening.^{2,6,8} Patients were randomized to receive either rosuvastatin 20mg or placebo.^{2,8} The endpoint focused on in this article was incidence of symptomatic VTE.² Overall results showed a statistically significant difference between the rosuvastatin and placebo groups in favor of rosuvastatin (hazard ratio 0.57, P = 0.007).² A comparison between groups looking at rate of first CVE or VTE also showed a significant difference in favor of rosuvastatin (hazard ratio 0.56, P<0.001).² With regard to this endpoint, numbers needed to treat were calculated for four and five years, which were 26 and 21 respectively.²

Although this study included a large population, participants were relatively healthy and overall not at high risk of developing VTE. Additional research is necessary to confirm these results and better define the patient population most likely to benefit from treatment.

References:

1. Haines, ST, Witt, DM, Nutescu, EA. Venous Thromboembolism. In: DiPiro, JT, Talbert, RL, Yee, GC, Matzke, GR, Wells, BG, Posey, ML, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw Hill; 2008:331 and 355.
2. Glynn, RJ, Danielson, E, Fonseca, FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med*. 2009;360:1851-61.
3. Talbert, RL. Hyperlipidemia. In: DiPiro, JT, Talbert, RL, Yee, GC, Matzke, GR, Wells, BG, Posey, ML, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw Hill; 2008:395.
4. Clinical Pharmacology. Tampa, FL. Available at: <http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2673&sec=monindi>. Updated April 9, 2009. Accessed June 19, 2009.
5. Mahley, RW, Bersot, TP. Drug Therapy for Hypercholesterolemia and Dyslipidemia. In: Brunton, LL, Lazo, JS, Parker, KL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. <http://www.accessmedicine.com.cuhs.creighton.edu/content.aspx?aID=945881>.
6. Ridker, PM, Danielson, E, Fonseca, FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207.
7. Vasan, RS, Benjamin, EJ, Sullivan LM, D'Agostino, RB. The Burden of Increasing Worldwide Cardiovascular Disease. In: Fuster, V, O'Rourke, RA, Walsh, RA, Poole-Wilson, P, eds. *Hurst's The Heart*. 12th ed. <http://www.accessmedicine.com/content.aspx?aID=3059745>.
8. Ridker, PM, Fonseca, FAH, Genest, J, et al. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol*. 2007;100:1659-1664.

Tamsulosin and Ophthalmic Adverse Events Following Cataract Surgery by Tamara Ruggles

Benign prostatic hyperplasia (BPH) is a common finding affecting 80 percent of men at age 80.¹ Patients may have no symptoms, but generally present with out-flow obstruction and/or bladder irritability. Patient complaints often include troublesome lower urinary tract (LUT) symptoms such as urinary frequency, urgency, nocturia, decreased urinary stream, and incomplete bladder emptying.¹ Treatment options include pharmacotherapy and surgery.^{1,2}

Alpha₁-adrenergic receptor blockers are considered first-line treatment for mild to moderate symptoms associated with BPH. They are thought to relieve BPH symptoms through relaxation of smooth muscle in the bladder neck and prostate which increases the rate of urinary flow and decreases the volume of postvoid urine. Tamsulosin is the only alpha-blocker selective for alpha_{1A}-receptors. Alpha_{1A}-receptors are also found in smooth muscle that dilates the iris. Blocking these receptors in the iris may inhibit mydriasis during cataract surgery leading to intraoperative floppy iris syndrome (IFIS). IFIS may sequentially increase the risk of cataract surgery complications. Reference materials have cautioned about the risk of IFIS associated with tamsulosin but do not discuss other adverse effects following cataract surgery.^{1,2,4}

Bell CM et al. recently published a retrospective cohort study on postoperative adverse effects following cataract surgery associated with tamsulosin or other alpha-blockers. Men 66 years of age and older who had cataract surgery between April 1, 2002 and June 16, 2007 were included in the study. Documented procedures occurring within 14 days of cataract surgery for the treatment of retinal detachment, lost lens or lens fragment, or endophthalmitis were used to identify postoperative adverse events. The healthcare databases from Ontario, Canada were used to collect information for the study.²

Patients with recent tamsulosin exposure (within 14 days of surgery) had a significantly increased risk of adverse events following cataract surgery compared to men with no exposure to alpha-blockers in the year prior to cataract surgery (95% confidence interval [CI] 1.22-4.43). Absolute risk was 4.8%; number needed to harm was 21. An increase in adverse events following cataract surgery was not found with remote exposure (15-364 days before cataract surgery) to tamsulosin or recent or remote exposure to other alpha-blockers including alfuzosin, doxazosin, prazosin, and terazosin.²

Recent safety warnings and an increase in clinical awareness may lead practitioners to discontinue tamsulosin before cataract surgery, but the efficacy and safety of this strategy is unknown. It should be noted that IFIS and other complications can occur months after stopping tamsulosin therapy. At this time, it is prudent for clinicians to talk with their patients about the risk of IFIS and to be prepared for possible adverse events in this population.

References

1. First Consult [database on the internet]. Available at: <http://www.mdconsult.com>. Accessed June 15, 2006.
2. Bell CM, Hatch WV, Fischer HD, et al. Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery. *JAMA*. 2009;301(19):1991-1996
3. Friedman AH. Tamsulosin and the intraoperative floppy iris syndrome. *JAMA*. 2009;301(19):2044-2045.
4. Wells BG, Dipiro JT, Schwinghammer TL, and Dipiro CV. Urologic Disorders. In: *Pharmacotherapy Handbook 7th* ed. New York, NY: McGraw-Hill; 2009.





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