Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

Cardiology

UNIVERSITY OF TORONTO

Special New Feature
Visit us at www.cardiologyupdate.ca for PowerPoint teaching slides on this topic

AN EDUCATIONAL PUBLICATION FROM THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

The Evolution of Stroke Prevention: Where are We Now? Where are We Going?

Originally presented by: Pavel Hamet, MD; Christian Constance, MD; Philip Teal, MD; and Alexander Turpie, MD

An educational report based on a symposium from the Canadian Cardiovascular Congress 2008

October 25 – 29, 2008 Toronto, Ontario

Discussed by: GORDON MOE, MD, FRCPC

Every year in Canada, 1 in 600 people develops an ischemic stroke. Stroke is the fourth leading cause of death and the first leading cause of major morbidity in Canada. Risk factors for stroke include nonmodifiable ones such as age and previous history of stroke, as well as modifiable ones such as obesity, diabetes, smoking, and hypertension. This issue of *Cardiology Scientific Update* reviews the risk factors for stroke, the current recommendations on preventive therapy for stroke, including blood pressure (BP) lowering and antiplatelet agents, and the strategies for future stroke prevention utilizing the anticoagulation pathways.

The evolution of stroke prevention

Stroke causes death and major morbidity, and only 20% of those who suffer from stroke recover their premorbid level of functioning. Since the stroke mortality rate is only 27%, this implies that most people with a stroke will have a neurological handicap. Stroke risk factors include age, personal or family history of stroke, male sex, as well as potentially modifiable factors such as smoking, diabetes, obesity, physical inactivity, increased left ventricular (LV) mass, and hypertension.[1-3]

Across Europe and North America, the prevalence of hypertension in a given country correlates with the stroke mortality of that country.[4] Thus, Finland and Germany have a higher prevalence of hypertension and a corresponding higher stroke mortality when compared with North America. Increasing BP is closely associated with an increased risk of death from stroke and long-term antihypertensive therapy significantly reduces cardiovascular (CV) events including stroke by 30%–40%.[5] The Shanghai Trial Of Nifedipine in the Elderly (STONE)[6] demonstrated that in 1632 hypertensive Chinese subjects aged 60-79 years, nifedipine reduced the relative risk (RR) for stroke and severe arrhythmia compared with placebo (1.0 to 0.41; 95% confidence interval [CI], 0.27-0.61). Currently, genome-wide linkage studies in hypertension are developing multiple novel approaches to more appropriately establish the genomic architecture of hypertension.[7] The further integration of genomics and transcriptomics with geoethnic background and environment will assist in resolving such complex disorders as hypertension.

The evolution of stroke prevention: antihypertensives

Approximately two-thirds of the worldwide cerebrovascular disease burden is due to suboptimal BP control and almost 70% of patients who experience their first stroke have a BP ≥140/90 mm Hg.[8] In the original cohort of participants in the Framingham Study (N=4897), who were stroke- and dementia-free at 55 years of age and who were followed biennially for up to 51 years (115 146 person-years), the lifetime risk (LTR) of stroke was high and remained similar at ages 55, 65, and 75 years (ie, ~1 in 5 for women and 1 in 6 for men). Importantly, participants with a normal BP (<120/80 mm Hg) had approximately half the LTR of stroke compared with those with high BP (≥140/90 mm Hg).[9]

Primary-prevention trials were conducted predominantly in patients with hypertension and examined stroke outcomes, which were defined as neurological deficits with symptoms lasting ≥24 hours and confirmed by examination or imaging.[10] The relative risk reductions (RRR) in stroke ranged from 20% to 57%, with the greatest reductions observed in trials with larger reductions in BP compared with placebo or the comparator. The recently published Hypertension in the Very Elderly Trial (HYVET), assigned 3845 patients from Europe, China, Australasia, and Tunisia (all ≥80 years of age and with sustained systolic BP of ≥160 mm Hg) to receive either the diuretic, indapamide, or matching placebo.[11] The angiotensin-converting enzyme (ACE) inhibitor, perindopril, was added, if necessary to achieve the target BP of 150/80 mm Hg. The primary endpoint was fatal or nonfatal stroke with a median follow-up of 1.8 years. At 2 years, BP was 15.0/6.1 mm Hg lower in the active treatment group versus the placebo group. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the rate of

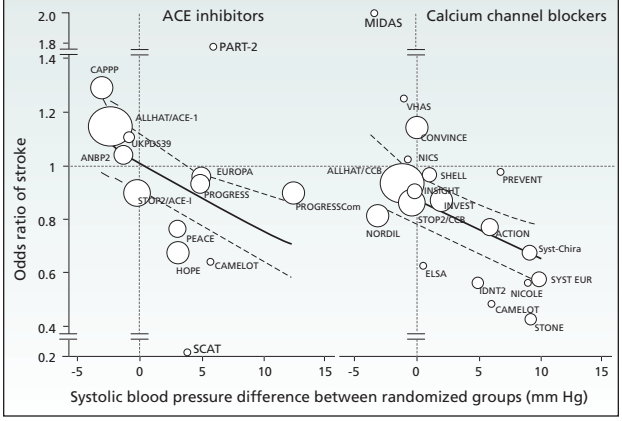
St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

fatal or nonfatal stroke (95% CI, -1 to 51; *P*=0.06) and a 39% reduction in death from stroke (95% CI, 1 to 62; *P*=0.05). These findings suggest that antihypertensive therapy reduces the risk of stroke in the elderly with hypertension. On the other hand, trials in patients with angina or established coronary artery disease (CAD) have not demonstrated benefits of treatment on stroke outcomes.[12-16] Interestingly, in a subgroup analysis of A Coronary disease Trial Investigating Outcome with Nifedipine (ACTION) gastrointestinal therapeutic system (GITS) in patients with baseline BP ≥140/90 mm Hg, treatment with nifedipine GITS was associated with a significant reduction in debilitating stroke by 33%.[10]

Several trials have provided insight into the role of antihypertensive therapy in the secondary prevention of stroke.[17] The Perindopril Protection against Recurrent Stroke Study (PROGRESS) was the first large-scale prospective BP study for secondary prophylaxis after stroke. It was designed to determine the effects of a BP-lowering regimen in hypertensive and nonhypertensive patients with a history of stroke or transient ischemic attack (TIA) within the previous 5 years. The trial examined 6105 individuals from 172 centres in Asia, Australasia, and Europe, who were randomized to active treatment or placebo. The active-treatment arm was a flexible regimen based on the ACE inhibitor, perindopril, with the addition of the diuretic, indapamide, at the discretion of treating physicians. For the primary outcome of total stroke (fatal or nonfatal), over 4 years, the active treatment reduced BP by 9/4 mm Hg, with 307 (10%) individuals in active treatment suffering a stroke, compared with 420 (14%) assigned placebo (RRR 28%; 95% CI, 17-38; *P*<0.0001). There were similar reductions in the risk of stroke in both the hypertensive and nonhypertensive subgroups (all *P*<0.01). Combination therapy with perindopril plus indapamide reduced BP by 12/5 mm Hg and stroke risk by 43% (95% CI, 30-54). Single-drug therapy, however, reduced BP by only 5/3 mm Hg and produced no discernable reduction in the risk of stroke. Although stroke survivors benefit from treatment whether or not they have hypertension at baseline, on the basis of these data, the reduced incidence of stroke appeared related to the BP reduction obtained by combination therapy, even though on study entry many patients were not hypertensive.[17] The Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS)[18] is the largest secondary stroke prevention trial to date, involving 20 332 subjects from 695 centres in 35 countries. All patients had a noncardioembolic ischemic stroke within the previous 120 days, and were randomized in a 2×2 factorial design fashion to receive acetylsalicylic acid (ASA, 25 mg) plus extended-release (ER) dipyridamole (200 mg) twice daily or clopidogrel (75 mg) once daily, as well as either telmisartan (80 mg/day) or placebo. During a mean follow-up of 2.5 years, the mean BP was 3.8/2.0 mm Hg lower in the telmisartan group than in the placebo group. A total of 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group had a subsequent stroke (hazard ratio [HR] in the telmisartan group, 0.95; 95% CI, 0.86 to 1.04; *P*=0.23).

To investigate whether protection from CAD and stroke conferred by ACE inhibitors and calcium channel blockers (CCBs) in hypertensive or high-risk patients may be explained by a specific drug regimen, 28 outcome trials for a total of 179 122 patients (9509 incident cases of CAD and 5971 cases of stroke) were examined in a meta-analysis.[19] In placebo-controlled trials, ACE inhibitors decreased the risk of CAD (*P*<0.001) and CCBs reduced stroke incidence (*P*<0.001). The risk of stroke was reduced by CCBs (*P*=0.041), but not by ACE inhibitors (*P*=0.15), as compared with diuretics/beta-blockers. Because heterogeneity between trials was significant, potential sources of heterogeneity were investigated by meta-regression. Prevention of CAD was explained by systolic BP reduction (*P*<0.001) and use of ACE inhibitors (*P*=0.028), whereas prevention of stroke was explained by systolic BP reduction (*P*=0.001) and use of CCBs (*P*=0.042). These findings confirm that BP lowering is fundamental for prevention of CAD and stroke. However, over and beyond BP reduction, CCBs appear superior to ACE inhibitors for preventing strokes, since every 10-mm Hg decrease in systolic BP leads to a 15% decrease in the risk of stroke (Figure 1).

Figure 1: Risk of stroke and blood pressure reduction



The 2008 Canadian Hypertension Education Program (CHEP) recommends to "strongly consider BP reduction in all patients after the acute phase of nondisabling stroke or TIA," and the preferred agents are a combination of ACE inhibitor and diuretic.[20] Furthermore, in patients with isolated systolic hypertension who are at particular risk for stroke, after lifestyle modification, it is recommended to use a thiazide diuretic, or long-acting angiotensin receptor blockers (ARBs), or dihydropyridine CCBs to reduce BP to <140/90 mm Hg.

The evolution of stroke prevention: oral antiplatelet agents

The role of oral antiplatelet agents in the management of stroke can be considered in the context of primary and secondary prevention, as well as in the management of acute stroke. ASA, the prototype antiplatelet agent, has been in clinical use as an antithrombotic for almost a half century. In primary prevention, aggregate data on men from the Physicians' Health Study,[21] British Doctors' Trial,[22] Hypertension Optimal Treatment (HOT) Trial,[23] and Primary Prevention Project[24] suggest that while ASA reduces the risk of nonfatal myocardial infarction (MI) by 32%, it leads to a nonsignificant increase in the risk of nonfatal stroke (RR 1.13; 95% CI, 0.96-1.33; *P*=0.15). On the other hand, aggregate data on women, from the Women's Health Study (WHS) in 39 876

initially healthy women,[25] and 5 other trials on patients with no prior history of MI, suggest that ASA reduces stroke by 19% (95% CI, 0.69 to 0.96; *P*=0.01), but with no reduction in MI (RR 0.99; 95% CI, 0.93 to 1.19; *P*=0.95). In the WHS, the prespecified subgroup analyses revealed that ASA significantly reduced the risk of ischemic stroke among women ≥65 years of age, as well as in those with hypertension and diabetes.[25]

The guidelines from the American Heart Association (AHA)/American Stroke Association Stroke Council recommend ASA for primary prevention of ischemic stroke in women if the benefits outweigh the treatment risks, but not in men.[26] Additional recommendations for women in the AHA Evidenced-Based Guidelines for Cardiovascular Disease Prevention in Women, 2007 Update[27] support the use of of ASA in high-risk women unless contraindicated and low-dose ASA for older women if BP is controlled and the benefits outweigh the risks of bleeding.

The recently published Prevention of Progression of Arterial Disease and Diabetes (POPADAD)[28] trial is a randomized, placebo-controlled trial of ASA and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease (PAD). The 1276 adults aged ≥40 years with type 1 or type 2 diabetes and an ankle-brachial pressure index of ≤0.99, but no symptomatic CV disease were randomized to one of the following: 100 mg ASA plus antioxidant capsule (n=320), ASA plus placebo capsule (n=318), placebo plus antioxidant capsule (n=320), or placebo plus placebo capsule (n=318). Two hierarchical composite primary endpoints were measured: death from CAD or stroke, nonfatal MI or stroke, or amputation above the ankle for critical limb ischemia; and death from CAD or stroke. Overall, 116 of 638 primary events occurred in the ASA groups compared with 117 of 638 in the non-ASA groups (18.2% vs 18.3%), HR 0.98 (95% CI, 0.76 to 1.26). Forty-three deaths from CAD or stroke occurred in the ASA groups compared with 35 in the non-ASA groups (6.7% vs 5.5%), HR 1.23 (95% CI, 0.79 to 1.93).[28]

For secondary prevention, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)[29] trial was a randomized, blinded, international trial designed to assess the relative efficacy of clopidogrel (75 mg/day) and ASA (325 mg/day) in reducing the risk of a composite outcome cluster of ischemic stroke, MI, or vascular death. The population studied was composed of patient subgroups with atherosclerotic vascular disease manifested as recent ischemic stroke, recent MI, or symptomatic PAD. Intention-to-treat analysis revealed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death compared with 5.83% among those treated with ASA. These rates reflect a statistically significant (*P*=0.043) RRR of 8.7% in favour of clopidogrel (95% Cl, 0.3-16.5); however, clopidogrel significantly reduced the RR of the composite outcome (23.8%) only in patients with PAD; data in this patient population drove the positive conclusions observed with clopidogrel. In addition, for PAD patients, clopidogrel revealed a statistically significant RR of 38.1% for the risk of MI, but there was no statistically significant effect on stroke.

The European Stroke Prevention Study 2 (ESPS 2)[30] was a randomized, placebo-controlled, double-blind trial to investigate the safety and efficacy of low-dose ASA, modified-release dipyridamole (ER-DP), and the 2 agents in combination for the secondary prevention of ischemic stroke. Over 2 years, there was a 12.5% (206 events/1,649 patients) event rate of stroke noted for ASA-treated patients and a 9.5% (157 events/1,650 patients) event rate for ASA/ER-DP-treated patients, with a difference in bleeding rates of 1.2% (20 events/1,649 patients) versus 1.6% (27 events/1,650 patients), respectively. The total event rates of stroke or death and bleeding events were 13.7% in the ASA-treated group and 11.1% in the ASA/ER-DP-treated group.

The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial[31] assessed whether the addition of ASA to clopidogrel could have greater benefits than clopidogrel alone in preventing vascular events with potentially higher bleeding risk. High-risk patients (N=7599) with recent ischemic stroke or TIA and at least 1 additional vascular risk factor, and receiving clopidogrel (75 mg/day), were randomized to ASA (75 mg/day) or placebo. The primary endpoint was a composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemia (including rehospitalization for TIA, angina pectoris, or worsening PAD). The addition of ASA to clopidogrel resulted in a significantly higher bleeding rate (increased RR of major bleed) that offset any significant beneficial effect in preventing stroke, MI, or vascular death. Compared with clopidogrel alone, combination therapy was not significantly more effective in reducing the risk of these vascular events. Finally, the recently published Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study[32] demonstrated no difference in efficacy between clopidogrel and ASA + ER-DP for preventing a second stroke.

The 8th Edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on treatment and prevention of stroke[33] recommended antiplatelet drugs including low-dose ASA, ASA-ER-DP, and clopidogrel as acceptable first-line agents. The AHA/American Stroke Association Council on Stroke recommendations[34] have also supported the use of clopidogrel over ASA for preventing ischemic stroke in survivors of stroke or TIA.

The evolution of stroke prevention: anticoagulants

Although antithrombotics have changed clinical practice, for oral anticoagulation, the vitamin K antagonist, warfarin, is currently the only option. Atrial fibrillation (AF) accounts for approximately 1 in 6 ischemic strokes (1 in 4 in elderly patients).[35] When compared with placebo, warfarin reduces the risk of stroke by 60% and its protection is superior to ASA[36] or to ASA + clopidogrel.[37] However, the use of warfarin is associated with limitations, such as the unpredictable pharmacokinetics and pharmacodynamics, requiring monitoring and frequent dose adjustments to maintain international normalized ratio (INR) within the therapeutic window, and the slow onset and offset of action.[38] As a result, these limitations may lead to undertreatment of patients with AF,[39] and they underscore the need for newer anticoagulants.

There are a number of targets for novel anticoagulants in the coagulation pathway. Tissue factor pathway inhibitor (TFPI) bound to Factor Xa inactivates the TF–Factor VIIa complex, preventing initiation of coagulation. Activated protein C (APC) degrades Factors Va and VIIIa, and thrombomodulin (soluble; sTM) converts thrombin (Factor IIa) from a procoagulant to a potent activator of protein C. Fondaparinux and idraparinux indirectly inhibit Factor Xa, requiring antithrombin (AT) as a cofactor. Direct

(AT-independent) inhibitors of Factor Xa include rivaroxaban (BAY 59-7939), LY517717, YM150, and DU-176b (all orally available) and DX-9065a (intravenous). The oral direct thrombin inhibitors include ximelagatran (now withdrawn from the market) and dabigatran; the latter is being extensively studied across a range of indications. Currently, >34 000 patients are involved in the REVOLUTION™ Phase III clinical trial program. RE-LY, the largest AF stroke outcomes trial to date, is comparing 2 blinded doses of dabigatran versus open-label warfarin (INR 2.0–3.0). The median treatment duration will be approximately 24 months with efficacy outcomes a composite of stroke and systemic embolism.[40]

Apixaban and rivaroxaban are the 2 oral direct Factor Xa inhibitors at the most advanced stage of clinical development. Rivaroxaban has predictable dose-proportional pharmacokinetics and pharmacodynamics in healthy subjects, and demonstrates no evidence of accumulation after multiple dosing.[41,42] To date, rivaroxaban is the most studied with >20 000 patients evaluated in completed Phase II programs and enrolled thus far in Phase III programs. Almost 50 000 patients are expected to be evaluated in total. The Phase III REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE (RECORD) program[43] comprises 4 large clinical studies of rivaroxaban 10 mg once daily on venous thromboembolism in patients undergoing major orthopedic surgery. The ROCKET-AF trial is a prospective, randomized, double-blind, noninferiority study that compares the effect of rivaroxaban and warfarin on stroke outcomes in patients with nonvalvular AF and other risk factors. This study will involve approximately 14 000 patients and more than 1200 sites.

If these trials reveal equivalent efficacy with warfarin, as well as easier dosing, the future of stroke prevention may be improved.

References

1. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ*. 2002;324:1570-1576.
2. Coca A, Messerli FH, Benetos A, et al. Predicting stroke risk in hypertensive patients with coronary artery disease: a report from the INVEST. *Stroke*. 2008;39:343-348.
3. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. *JAMA*. 2002;288:1388-1395.
4. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*. 2003;289:2363-2369.
5. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2000;356:1955-1964.
6. Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens*. 1996;14:1237-1245.
7. Hamet P, Seda O. Current status of genome-wide scanning for hypertension. *Curr Opin Cardiol*. 2007;22:292-297.
8. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.
9. Seshadri S, Beiser A, Kelly-Hayes M, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. 2006;37:345-350.
10. Bangalore S, Messerli FH. A review of stroke in patients with hypertension and coronary artery disease: Focus on calcium channel blockers. *Int J Clin Pract*. 2006;60(10):1281-1286.
11. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-1898.
12. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002;359:1269-1275.
13. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.
14. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217-2225.
15. Pitt B, O'Neill B, Feldman R, et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol*. 2001;87:1058-1063.
16. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364:849-857.
17. PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001; 358:1033-1041.
18. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med*. 2008;359:1225-1237.
19. Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension*. 2005;46(2):386-392.
20. Khan NA, Hemmelgarn B, Herman RJ, et al. The 2008 Canadian Hypertension Education Program recommendations for the management of hypertension: part 2 – therapy. *Can J Cardiol*. 2008;24(6): 465-475.
21. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med*. 1989;321:129-135.
22. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)*. 1988;296:313-316.
23. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755-1762.
24. de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet*. 2001;357:89-95.
25. Ridker PM, Cook NR, Lee IM,et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-1304.
26. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(6):1583-1633.
27. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115(11):1481-1501.
28. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.
29. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
30. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A; European Stroke Prevention Study. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1-13.
31. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331-337.
32. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238-1251.
33. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):630S-669S.
34. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(2):577-617.
35. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-988.
36. Lip GY, Hart RG, Conway DS. Antithrombotic therapy for atrial fibrillation. *BMJ*. 2002;325:1022-1025.
37. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903-1912.
38. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:204S-233S.
39. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131:927-934.
40. Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) with dabigatran etexilate. Available at: www.clinicaltrials.gov/ct2/show/NCT00262600. Accessed January 15, 2009.
41. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939–an oral, direct Factor Xa inhibitor--after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol*. 2005;61:873-880.
42. Perzborn E, Strassburger J, Wilmen A, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct Factor Xa inhibitor. *J Thromb Haemost*. 2005;3:514-521.
43. Eriksson BI, Borris LC, Dahl OE, et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation*. 2006;114:2374-2381.

Dr. Moe has stated that he has no disclosures to announce in association with the contents of this issue.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Bayer Canada to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.