

A SELECTION OF TEN CURRENT READINGS ON ATHEROTHROMBOSIS AVAILABLE AS FREE FULL-TEXT (SOME REQUIRING PAYMENT)

Selection of readings made by A/Prof Goh Lee Gan

PRIMARY STROKE PREVENTION

Reading 1

Ezekowitz JA, Straus SE, Majumdar SR, McAlister FA. Stroke: strategies for primary prevention. Am Fam Physician. 2003 Dec 15;68(12):2379-86

<http://www.aafp.org/afp/20031215/2379.pdf> ([free full text](#))

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ABSTRACT

Stroke is a leading cause of morbidity and mortality in North America. Primary prevention of stroke includes lifestyle modifications and measures to control blood pressure, cholesterol levels, diabetes mellitus, and atrial fibrillation. Lowering blood pressure in patients with hypertension prevents both hemorrhagic and ischemic stroke (relative risk reduction, 35 to 45 percent). Observational studies suggest that higher cholesterol levels are associated with an increased risk of ischemic stroke, and treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) may reduce the risk of fatal and nonfatal stroke by 25 percent. Although high-quality evidence linking tighter glucose control with stroke reduction is lacking, good glucose control and aggressive treatment of hypertension and hyperlipidemia in patients with diabetes mellitus are recommended. The risk of stroke in patients with atrial fibrillation and the role of anticoagulation depend on factors such as age and the presence of comorbid conditions. Controversy exists about the roles of angiotensin-converting enzyme inhibitors and aspirin in the primary prevention of stroke.

Reading 2

Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Cardiorespiratory fitness and the risk for stroke in men. Arch Intern Med. 2003 Jul 28; 163(14):1682-8.

<http://archinte.ama-assn.org/cgi/content/full/163/14/1682>

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ABSTRACT

BACKGROUND: Low cardiorespiratory fitness is considered to be a major public health problem. We examined the relationship of cardiorespiratory fitness, as indicated by maximum oxygen consumption VO (2) max with subsequent incidence of stroke. We also compared VO (2) max with conventional risk factors as a predictor for future strokes.

METHODS: Population-based cohort study with an average follow-up of 11 years from Kuopio and surrounding communities of eastern Finland. Of 2011 men with no stroke or pulmonary disease at baseline who participated in the study, 110 strokes occurred, of which 87 were ischemic. The VO (2) max was measured directly during exercise testing at baseline.

RESULTS: The relative risk for any stroke in unfit men VO (2) max, <25.2 mL/kg per minute) was 3.2 (95% confidence interval [CI], 1.71-6.12; P<.001; P<.001 for the trend across the quartiles); and for ischemic stroke, 3.50 (95% CI, 1.66-7.41; P =.001; P<.001 for trend across the quartiles), compared with fit men VO(2)max, >35.3 mL/kg per minute), after adjusting for age and examination year. The associations remained statistically significant after further adjustment for smoking, alcohol consumption, socioeconomic status, energy expenditure of physical activity, prevalent coronary heart disease, diabetes, systolic blood pressure, and serum low-density lipoprotein cholesterol level for any strokes or ischemic strokes. Low cardiorespiratory fitness was comparable with systolic blood pressure, obesity, alcohol consumption, smoking, and serum low-density lipoprotein cholesterol level as a risk factor for stroke.

CONCLUSIONS: Our findings show that low cardiorespiratory fitness was associated with an increased risk for any stroke and ischemic stroke. The VO (2) max was one of the strongest predictors of stroke, comparable with other modifiable risk factors.

Reading 3

Messerli FH, Grossman E, Lever AF. Do thiazide diuretics confer specific protection against strokes? Arch Intern Med. 2003 Nov 24; 163(21):2557-60.

<http://archinte.ama-assn.org/cgi/content/full/163/21/2557>

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ABSTRACT

Several large studies have suggested that therapy with thiazide diuretics confers a particular benefit in reducing the risk of strokes that seem to be, at least to some extent, independent of the blood pressure-lowering effect. Such a cerebroprotective effect was documented not only with monotherapy but also when diuretics were used in combination with other drugs. The cerebroprotective effect does not seem to be shared by other drug classes, such as the beta-blockers or the angiotensin-converting enzyme inhibitors, in patients without manifest cardiovascular disease. Since stroke is one of the most devastating sequelae of high blood pressure, our data strongly favor the use of low-dose diuretics either as initial therapy or in combination in all hypertensive patients at risk for cerebrovascular disease.

Reading 4

Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. Arch Intern Med. 2003 Mar 24; 163(6):669-76.

<http://archinte.ama-assn.org/cgi/content/full/163/6/669>

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ABSTRACT

BACKGROUND: Previous overviews suggested that hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins), but not other lipid-lowering therapy (LLT), may reduce stroke incidence in coronary patients.

OBJECTIVE: To investigate the amplitude and sources of heterogeneity of LLT effects on stroke prevention.

METHODS: We searched the literature from 1966 to 2001 and then conducted a meta-analysis including randomized trials of primary and secondary coronary heart disease prevention, testing statins, nonstatin drugs, diet, or other interventions and providing data on stroke incidence.

RESULTS: The meta-analysis (38 trials, 83 161 patients, mean follow-up of 4.7 years) showed a significant relative risk reduction (RRR) of strokes by LLT of 17% ($P<.001$), without significant heterogeneity between trials and between subgroups according to either the type of prevention (primary or secondary) or the type of LLT. The most substantial effects were obtained, however, with statins (RRR, 26%). Effect model analysis showed that treatment benefit appeared constant whatever the risk of stroke, suggesting that LLT may be effective in a population with a higher risk of stroke. Weighted regression showed a significant correlation between RRR of stroke and total cholesterol levels (baseline, final, and change). Only final cholesterol allowed clear separation between benefit ($RRR>0$) and no effect ($RRR<0$) of LLT on stroke incidence, with a cutoff for benefit of 232 mg/dL (6.0 mmol/L).

CONCLUSION: Lipid-lowering therapy reduces stroke incidence in coronary patients, especially when total cholesterol level is lowered to less than 232 mg/dL (6.0 mmol/L), which explains the best results being obtained with statins.

STROKE COMPLICATIONS IN SINGAPORE SETTING

Reading 5

Doshi VS, Say JH, Young SH, Doraisamy P. Complications in stroke patients: a study carried out at the Rehabilitation Medicine Service, Changi General Hospital. Singapore Med J. 2003 Dec; 44(12):643-52.

<http://www.sma.org.sg/smj/4412/4412a5.pdf> (free full text)

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ABSTRACT

AIM: The aim of this study was to look at the type and frequencies of complications after an acute stroke in an inpatient rehabilitation setting. We also looked at the type of complications which required the transfer of patient care back to the primary referring physician.

MATERIALS AND METHODS: A retrospective review of case notes of patients transferred to the rehabilitation team was conducted. The study period was a six-month period from the beginning of January 2001 to the end of June 2001. A list of complications was made. Each pre-determined complication was then defined. The frequency of each complication was then calculated.

RESULTS: A total of 140 case notes were reviewed. The overall complication rate was 54.3%. The more common complications, in order, from highest to lowest frequencies, were: constipation (complicating 22.9% of strokes); acute retention of urine (ARU, 20.9%); urinary tract infections (UTI, 14.3%); depression (9.3%); and limb pain (8.6%). Females were more likely to have UTI ($p=0.038$), ARU ($p=0.002$) and depression ($p=0.018$). Patients 65 years and above were more likely to suffer multiple complications although the results did not reach statistical significance ($p=0.055$). The care for eight patients (5.7% of patients with complications) had to be transferred back to the primary referring team or physician.

CONCLUSIONS: Complications post stroke are common. Some patients required transfer of care back to the primary referring physician. A pro-active approach is ideal in all post stroke patients, in order to identify and treat any complications early, thereby, improving outcome and reducing costs.

CARDIOVASCULAR DISEASE PREVENTION

Reading 6

Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. JAMA. 2003 Apr 2; 289(13):1659-66.

<http://jama.ama-assn.org/cgi/content/full/289/13/1659>

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ABSTRACT

CONTEXT: People older than 65 years are the fastest-growing segment of the population and account for the majority of cardiovascular disease (CVD) morbidity, mortality, and health care expenditures. Additionally, the influence of dietary habits on risk may be less pronounced in elderly persons, when atherosclerosis is more advanced. However, few data address the influence of diet on CVD risk in this population.

OBJECTIVE: To determine whether fiber consumption from fruit, vegetable, and cereal sources (including whole grains and bran) is associated with incident CVD in elderly persons.

DESIGN: Prospective cohort study conducted from 1989 to June 2000.

SETTING AND PARTICIPANTS: Population-based, multicenter study among 3588 men and women aged 65 years or older and free of known CVD at baseline in 1989-1990. Usual dietary fiber consumption was assessed at baseline (mean participant age, 72 years) using a 99-item food frequency questionnaire.

MAIN OUTCOME MEASURE: Incident CVD (combined stroke, ischemic heart disease death, and nonfatal myocardial infarction).

RESULTS: During 8.6 years mean follow-up, there were 811 incident CVD events. After adjustment for age, sex, education, diabetes, ever smoking, pack-years of smoking, daily physical activity, exercise intensity, alcohol intake, and fruit and vegetable fiber consumption, cereal fiber consumption was inversely associated with incident CVD (P for trend = .02), with 21% lower risk (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.62-0.99) in the highest quintile of intake, compared with the lowest quintile. In similar analyses, neither fruit fiber intake (P for trend = .98) nor vegetable fiber intake (P for trend = .95) were associated with incident CVD. When CVD events were separately evaluated, higher cereal fiber intake was associated with lower risk of total stroke and ischemic stroke and a trend toward lower risk of ischemic heart disease death. In a post hoc analysis, dark breads such as wheat, rye, or pumpernickel were associated with a lower risk of incident CVD (HR, 0.76; 95% CI, 0.64-0.90) rather than cereal fiber from other sources.

CONCLUSIONS: Cereal fiber consumption late in life is associated with lower risk of incident CVD, supporting recommendations for elderly individuals to increase consumption of dietary cereal fiber.

ANTIHYPERTENSIVE THERAPY OUTCOME IN CARDIOVASCULAR DISEASE

Reading 7

Bruce M. Psaty, MD, PhD; Thomas Lumley, PhD; Curt D. Furberg, MD, PhD; Gina Schellenbaum; Marco Pahor, MD; Michael H. Alderman, MD; Noel S. Weiss, MD, DrPH Health Outcomes Associated With Various Antihypertensive Therapies Used as First-Line Agents Network Meta-analysis JAMA. 2003; 289:2534-2544.

<http://jama.ama-assn.org/cgi/content/full/289/19/2534>

ABSTRACT

CONTEXT: Establishing relative benefit or harm from specific antihypertensive agents is limited by the complex array of studies that compare treatments. Network meta-analysis combines direct and indirect evidence to better define risk or benefit.

OBJECTIVE: To summarize the available clinical trial evidence concerning the safety and efficacy of various antihypertensive therapies used as first-line agents and evaluated in terms of major cardiovascular disease end points and all-cause mortality.

DATA SOURCES AND STUDY SELECTION: We used previous meta-analyses, MEDLINE searches, and journal reviews from January 1995 through December 2002. We identified long-term randomized controlled trials that assessed major cardiovascular disease end points as an outcome. Eligible studies included both those with placebo-treated or untreated controls and those with actively treated controls.

DATA EXTRACTION: Network meta-analysis was used to combine direct within-trial between-drug comparisons with indirect evidence from the other trials. The indirect comparisons, which preserve the within-trial randomized findings, were constructed from trials that had one treatment in common.

DATA SYNTHESIS: Data were combined from 42 clinical trials that included 192 478 patients randomized to 7 major treatment strategies, including placebo. For all outcomes, low-dose diuretics were superior to placebo: coronary heart disease (CHD; RR, 0.79; 95% confidence interval [CI], 0.69-0.92); congestive heart failure (CHF; RR, 0.51; 95% CI, 0.42-0.62); stroke (RR, 0.71; 0.63-0.81); cardiovascular disease events (RR, 0.76; 95% CI, 0.69-0.83); cardiovascular disease mortality (RR, 0.81; 95% CI, 0.73-0.92); and total mortality (RR, 0.90; 95% CI, 0.84-0.96). None of the first-line treatment strategies – b-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), a-blockers, and angiotensin receptor blockers – was significantly better than low-dose diuretics for any outcome. Compared with CCBs, low-dose diuretics were associated with reduced risks of cardiovascular disease events (RR, 0.94; 95% CI, 0.89-1.00) and CHF (RR, 0.74; 95% CI, 0.67-0.81). Compared with ACE inhibitors, low-dose diuretics were associated with reduced risks of CHF (RR, 0.88; 95% CI, 0.80-0.96), cardiovascular disease events (RR, 0.94; 95% CI, 0.89-1.00), and stroke (RR, 0.86; 0.77-0.97). Compared with b-blockers, low-dose diuretics were associated with a reduced risk of cardiovascular disease events (RR, 0.89; 95% CI, 0.80-0.98). Compared with a-blockers, low-dose diuretics were associated with reduced risks of CHF (RR, 0.51; 95% CI, 0.43-0.60) and cardiovascular disease events (RR, 0.84; 95% CI, 0.75-0.93). Blood pressure changes were similar between comparison treatments.

CONCLUSIONS: Low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality. Clinical practice and treatment guidelines should reflect this evidence, and future trials should use low-dose diuretics as the standard for clinically useful comparisons.

PERIPHERAL VENOUS DISEASE

Reading 10

Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG, Paulson R, Wong T, Bauer KA, Schwartz BA, Miletich JP, Bounameaux H, Glynn RJ; PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003 Apr 10; 348(15):1425-34.

<http://content.nejm.org/cgi/reprint/348/15/1425.pdf>

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ABSTRACT

BACKGROUND: Standard therapy to prevent recurrent venous thromboembolism includes 3 to 12 months of treatment with full-dose warfarin with a target international normalized ratio (INR) between 2.0 and 3.0. However, for long-term management, no therapeutic agent has shown an acceptable benefit-to-risk ratio.

METHODS: Patients with idiopathic venous thromboembolism who had received full-dose anticoagulation therapy for a median of 6.5 months were randomly assigned to placebo or low-intensity warfarin (target INR, 1.5 to 2.0). Participants were followed for recurrent venous thromboembolism, major hemorrhage, and death.

RESULTS: The trial was terminated early after 508 patients had undergone randomization and had been followed for up to 4.3 years (mean, 2.1). Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism (7.2 per 100 person-years), as compared with 14 of 255 patients assigned to low-intensity warfarin (2.6 per 100 person-years), a risk reduction of 64 percent (hazard ratio, 0.36 [95 percent confidence interval, 0.19 to 0.67]; $P < 0.001$). Risk reductions were similar for all subgroups, including those with and those without inherited thrombophilia. Major hemorrhage occurred in two patients assigned to placebo and five assigned to low-intensity warfarin ($P = 0.25$). Eight patients in the placebo group and four in the group assigned to low-intensity warfarin died ($P = 0.26$). Low-intensity warfarin was thus associated with a 48 percent reduction in the composite end point of recurrent venous thromboembolism, major hemorrhage, or death. According to per-protocol and as-treated analyses, the reduction in the risk of recurrent venous thromboembolism was between 76 and 81 percent,

CONCLUSIONS: Long-term, low-intensity warfarin therapy is a highly effective method of preventing recurrent venous thromboembolism.

STATINS IN ACUTE CORONARY SYNDROMES

Reading 8

Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med. 2004 [Epub ahead of print]

<http://content.nejm.org/cgi/reprint/NEJMoa040583v1.pdf> (free full text)

ABSTRACT

BACKGROUND: Lipid-lowering therapy with statins reduces the risk of cardiovascular events, but the optimal level of low-density lipoprotein (LDL) cholesterol is unclear.

METHODS: We enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Follow-up lasted 18 to 36 months (mean, 24).

RESULTS: The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group ($P<0.001$). Kaplan-Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin ($P=0.005$; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.

CONCLUSIONS: Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.

PERIPHERAL ARTERIAL DISEASE

Reading 9

Mohler ER 3rd. Peripheral arterial disease: identification and implications. Arch Intern Med. 2003 Oct 27; 163(19):2306-14.

<http://archinte.ama-assn.org/cgi/content/full/163/19/2306>

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ABSTRACT

Peripheral arterial disease (PAD) is most commonly a manifestation of systemic atherosclerosis in which the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque. Patients with PAD are at triple the risk of all-cause mortality and at more than 6 times the risk of death from coronary heart disease as those without the disease, yet PAD is probably the most underdiagnosed and least aggressively managed atherosclerotic disease. In the diagnosis of PAD, a detailed history and physical examination are extremely important, although limited by a lack of consistent sensitivity and specificity. Other office-based noninvasive tests, including the ankle-brachial index, can be easily performed to confirm the diagnosis and help stratify the risk. The ankle-brachial index correlates well with disease severity and functional symptoms and can also be used to assess disease progression and to predict cardiovascular and cerebrovascular mortality. Once diagnosed, risk factor modification, symptomatic relief, and secondary prevention strategies with antiplatelet agents form the core of medical management of PAD.