Different Locations of Atherosclerosis - Different Risk Factors, Different Therapies?

Gordon D.O. Lowe

Professor of Vascular Medicine, University Department of Medicine
Royal Infirmary, Glasgow, UK

Key Words

Atherosclerosis · Thrombosis · Smoking · Blood pressure · Cholesterol

Copyright © 2004 S. Karger AG, Basel

Introduction

Atherosclerosis is a strikingly focal disease, occurring at certain points in the arterial tree. Clinical consequences usually occur in the heart, head, abdomen and lower limb; and are usually precipitated by rupture of arterial plaques, with superadded thromboembolism (atherothrombosis). The major clinical consequences are:

- Coronary Heart Disease (CHD) - stable angina, acute coronary syndromes (unstable angina, myocardial infarction (MI), sudden coronary death), heart failure
- Head - stroke, transient cerebral or ocular ischaemic attacks (TIA's), vascular dementia
- Abdomen - aortic aneurysm, renal artery stenosis, intestinal ischaemia
- Lower limb (Peripheral Arterial Disease, PAD) - intermittent claudication, critical limb ischaemia

Among developed countries, advances in treatment of these different clinical presentations of atherothrombosis has increasingly led to specialist referral and specialist follow-up. There is good evidence that patients with acute

cardiac ischaemia have a better clinical outcome if they are immediately referred to coronary care units; and if rehabilitation and secondary prevention are organised by cardiac nurses. Likewise, patients with acute stroke or TIA have a better clinical outcome if referred early to stroke units and organised stroke services for early management, rehabilitation and secondary prevention. Critical limb ischaemia and symptomatic aortic aneurysm require urgent referral to peripheral vascular units.

However, increasing specialist management often causes healthcare professionals to view the patient as a "heart", "stroke", or "peripheral" problem; ignoring the systemic nature of atherothrombosis and its three consequences:

- A patient with clinically evident disease at one site is at increased risk of further clinical events not only at that site, but also at other sites
- Risk factors for disease at one site are usually risk factors for disease at other sites
- Secondary prevention is generally similar for disease presenting at different sites
- This review considers the evidence for these three statements in turn.

KARGER

Fax +41 61 306 12 34
E-Mail: karger@karger.ch
www.karger.com

© 2004 S. Karger AG, Basel
1424-8832/04/0336-0262\$21.00/0

Accessible online at:
www.karger.com/pht

Prof. Gordon DO Lowe, Professor of Vascular Medicine
University of Glasgow, University Department of Medicine
3rd Floor, QEB, Royal Infirmary
Glasgow, G31 2ER, UK

Tel: +44 141 211 5412; Fax: +44 141 211 0414; E-mail: gd1j@clinmed.gla.ac.uk

Clinical Ischaemic Disease at One Site Carries an Increased Risk of Atherothrombotic Disease and Ischaemic Events at Another Site

In 1965, Mitchell and Schwartz [1] showed significant correlations between atherosclerosis in the coronary, carotid and iliac arteries, in a large autopsy series.

A study of coronary arteriography in patients undergoing elective surgery for peripheral arterial disease observed a high prevalence of coronary artery disease [2]. The increasing development of ultrasound to detect atherosclerosis (symptomatic or asymptomatic) in peripheral and carotid arteries has allowed correlation of such measures with each other and with coronary heart disease (symptomatic or asymptomatic: e.g. electrocardiographic), not only in symptomatic populations, but also in samples of the general population. For example, in the Edinburgh Artery Study, both claudication and severe asymptomatic PAD (Ankle Brachial Pressure Index, ABPI < 0.7) were associated with evidence of CHD in over 50% of patients [3]. Conversely, 40% of hospitalised patients with CHD had a history of PAD or ABPI < 0.9 in a recent series [4]. About one-third of patients with symptomatic PAD have carotid atherosclerosis [5]; and conversely patients with stroke often have evidence of PAD [6]. There is postmortem and epidemiological evidence for an association between CHD and stroke; some of this association is causal (cerebral embolism from intracardiac thrombus) rather than due to coexisting atherosclerosis in the coronary and cerebral circulations [7]. However, it is likely that much of the association of atherothrombotic disease at different sites reflects the common influences of shared risk factors and mechanisms [8].

Turning from arterial disease to clinical ischaemic events, an epidemiological association between risk of events at one site and risk of events at other sites was one of the early findings of the Framingham Study [9]. Subsequent prospective studies - both epidemiological studies [10] and clinical trials [11] - have confirmed that patients with symptomatic PAD (even in the absence of a history of myocardial infarction or ischaemic stroke) have a similar risk of cardiovascular death as do patients with a history of CHD or cerebrovascular disease. All patients with clinical evidence of atherothrombosis at one site have an increased risk of MI, stroke or cardiovascular death.

Clearly, it is important for all clinicians to identify persons at high risk of any type of ischaemic event. While most attention has been paid traditionally to CHD prevention (perhaps because it is a major cause of premature death), in the ageing populations of developed countries the relative burden of all vascular events should be considered. This has rarely been measured in the same population at the same

time. In the recent Oxford Vascular Study [12,13] of 90,542 persons, 50% of all incident and recurrent vascular events were CHD, 40% were cerebrovascular, and 10% were peripheral (critical limb ischaemia, acute aortic pathology, or acute bowel ischaemia [12]. While cardiologists have tended to assume that "secondary prevention" refers to prevention of heart attacks, stroke doctors interpret this term as prevention of strokes, and doctors of all types tend to neglect prevention of cardiovascular events in patients whose clinical evidence of ischaemia is only PAD [14], there is increasing evidence that "secondary prevention" of all major vascular events is appropriate, wherever atherothrombosis is clinically manifest.

Risk Factors for Disease at One Site are Usually Risk Factors for Disease at Other Sites

Major cardiovascular risk factors (defined as variables associated with risk, regardless of causality) for CHD [15]; are generally also risk factors for stroke [7] and for PAD [16].

Age and Sex

The incidence and prevalence of all three sites of disease increase exponentially with age in both men and women. In the Framingham Study of 7733 participants aged 40-94 examined between 1971 and 1975, the lifetime risk of CHD at age 40 was one in two for men, and one in three for women; and at age 70 it was still one in three for men and one in four for women [17]. The increased risk of CHD in men appears largely the result of environmental factors (e.g. fat consumption), rather than a protective effect of oestrogen [18]. Indeed, randomised controlled trials of hormone replacement therapy in postmenopausal women have shown increased risk of CHD, as well as of stroke [19]. In contrast, there is no major sex difference in risk of stroke or PAD [7,17].

Smoking, blood pressure and cholesterol

Tobacco-smoking (cigarette, pipe or cigar), blood pressure, and serum total cholesterol are the three classical risk factors for CHD, ischaemic stroke, and PAD, as identified over 30 years ago in the Framingham Study [9], and since confirmed in many observational studies and meta-analyses [7,15,20]. While it is widely believed that, together, they account for only about half of CHD cases, a recent report from the British Regional Heart Study [20] showed that adjustment for regression dilution (which underestimates blood pressure and cholesterol gradients), and taking account of previous active smoking and possible smoking, increased the population attributable risk fraction for these

three risk factors combined to over 80%. This emphasises that population-wide control of these risk factors is crucial for effective CHD prevention (primary and secondary) and probably also for prevention of ischaemic stroke and PAD. "Ideal" targets in developed countries [15] are therefore:

- No active or passive smoking
- Blood pressure less than 110 mmHg systolic and 70mmHg diastolic
- Serum total cholesterol <5.2 mmol/L (lower in secondary prevention - see below)

There is increasing evidence that reductions in the proportion of smokers in populations, and in mean levels of total cholesterol and systolic and diastolic blood pressures, are associated with reductions in CHD [15] and in stroke [13].

Smoking shows a stronger association with PAD than CHD or stroke, and especially with risk of critical limb ischaemia and amputation [16,21]. All persons with PAD, CHD or stroke should be strongly encouraged to stop smoking (or at least reduce it, because the risk is dose-dependent). In addition to advice and support (including access to smoking cessation clinics, if available), nicotine replacement therapy and bupropion increase the chances of success [22].

Blood pressure reduction guidelines are widely available [15]. There is increasing evidence that most commonly-used groups of antihypertensive drugs are similarly effective in prevention of cardiovascular events; and that two or three types of drug are frequently required to achieve target blood pressure levels: lower doses minimise the incidence of adverse effects [23,24]. Patients with PAD benefit as much from blood pressure reduction as other groups of patients, e.g. in the HOPE trial [25].

Cholesterol reduction is most effectively achieved by statins, which have been shown in the Heart Protection Study (simvastatin 40mg/day) to reduce the risks of MI, stroke and cardiovascular death, not only in patients with clinical evidence of CHD, but also in patients with ischaemic stroke or PAD [26]. As in other studies, the benefit from statins was unrelated to baseline cholesterol level [26], hence statins are indicated in secondary prevention (and in primary prevention in high-risk persons [15]) regardless of baseline cholesterol level. In Western countries, all cholesterol levels are "too high", and cholesterol is a poor predictor of benefit from its reduction. Baseline cholesterol should however be measured, to establish concordance with statin therapy (target reduction 25%), and as a possible indicator of familial hypercholesterolaemia if very high. More widespread use of statin therapy may be facilitated by reduced costs: some statins are now off-patent, and in some countries are licensed for over-the-counter avail-

ability; and routine monitoring of liver function tests and creatine kinase is no longer indicated in the absence of baseline evidence of liver disease and in the absence of symptoms suggesting myopathy.

There is a positive association of serum total cholesterol with ischaemic stroke (but not haemorrhagic stroke) in observational studies [27]. Consistent with this observation, the Heart Protection Study observed that statin therapy rapidly reduced the incidence of ischaemic strokes and TIA's as well as CHD events, with no apparent effect on cerebral haemorrhage, even among individuals without high cholesterol levels [27]. The reduction in total stroke was not significant in patients with baseline cerebrovascular disease (relative risk 0.98, 95% CI 0.79-1.22); however the 19% (SE 12; $p=0.1$) proportional reduction in ischaemic stroke did not differ from the 34% (SE 7; $p<0.0001$) proportional reduction in other high-risk trial participants (heterogeneity $p=0.2$).

Exercise, obesity and diabetes

Low regular leisure-time exercise is associated with increased risk of CHD, stroke and PAD [15,28,29], partly because (together with increased calorie intake) it leads to obesity, insulin resistance and type 2 diabetes mellitus (which carries a threefold increased risk of CHD, stroke and PAD). In Western countries, the epidemic of sedentary behaviour and increased calorie intake as "fast food" is predicted to cause a global epidemic of obesity, diabetes and cardiovascular disease during the twenty-first century, and behaviour change is urgently required [15,30]. Diabetes is a particular risk factor for critical limb ischaemia in PAD, due to peripheral neuropathy and risk of ulceration and infection [16,21].

All patients with symptomatic CHD, stroke and PAD should be encouraged to exercise, unless severely disabled. In addition to its value in secondary prevention, regular exercise plays an important role in rehabilitation after MI and stroke; and increases walking distance in claudicants [22]. All obese patients should be encouraged to lose weight. Detection and control of diabetes is also mandatory in all patients with CHD, stroke and PAD.

Other risk factors [15,31]

Homocysteine levels showed similar associations with CHD, ischaemic stroke and PAD in meta-analyses of prospective studies [32]. Similar associations with the MTHFR mutation, which is associated with increased plasma homocysteine levels, suggest that they may be of causal significance [33]. However, the first large randomised controlled trial of vitamin supplementation in secondary prevention (in stroke patients) was negative [34], hence causality is unproven.

Fibrinogen levels showed similar associations with CHD and stroke in the Fibrinogen Studies Collaboration, a meta-analysis of individual data from prospective studies [35]. There are similar associations for PAD [36]. A causal role for fibrinogen in cardiovascular disease is unproven.

C-reactive protein levels are associated with risk of CHD in a meta-analysis of prospective studies, although the association is weaker than previously suggested, possibly due to selective publication bias [37]. A causal role is again unproven.

Congenital thrombophilias

A recent meta-analysis suggests that the Factor V Leiden and prothrombin 20120A mutations, which are associated with increased risk of venous thromboembolism, are also weakly associated with increased risk of CHD, stroke and PAD, especially in the young and in women [38].

Management of Atherothrombosis at Different Sites

From the preceding section, it can be concluded that risk factor assessment and secondary prevention of atherothrombosis is similar in patients presenting with CHD, ischaemic stroke or PAD.

Antiplatelet therapy is also similarly effective in secondary prevention in patients with chronic CHD, ischaemic stroke or PAD [39]. Aspirin (75-300mg/day) is effective and inexpensive; clopidogrel is an effective alternative for patients in whom aspirin is contra-indicated or not tolerated; and dipyridamole is an effective alternative in similar

patients with TIA or stroke [39]. The addition of clopidogrel (or intravenous IIb/IIIa antagonists) to aspirin produces additional benefit in non-ST elevation MI acute coronary syndromes and in percutaneous coronary interventions [39-41]. The addition of dipyridamole to aspirin may produce additional benefit in TIA or stroke [39,42]. Further comparative studies of antiplatelet monotherapy (or combined therapy) are currently in progress in patients with CHD, ischaemic stroke, or PAD.

Heparins are of proven value in patients with acute coronary syndromes; however their efficacy and safety appears not of net benefit in acute stroke; and requires further investigation in PAD. Likewise thrombolysis is of proven value in patients with evolving acute MI; but its balance of efficacy and safety remains controversial in acute stroke and in critical limb ischaemia. It is likely that the balance of benefits and risks of heparin and thrombolysis is less favourable in evolving cerebral infarction, because ischaemic softening of the delicate brain occurs early (predisposing to cerebral haemorrhage) compared to the "harder" muscles of the heart and brain.

Conclusion

The systemic nature of atherothrombosis should lead to a more consistent approach to risk factor evaluation and secondary prevention, regardless of the site of clinical presentation.

References

- Mitchell JRA, Schwarz CJ. Arterial disease. Oxford: Blackwell Scientific, 1965.
- Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients - a classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; 199: 223-233
- Fowkes FGR, Housely E, Cawood EHH, et al. Edinburgh Artery Study; prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991; 20: 384-392
- Dieter RS, Tomasson J, Gusjonsson T, Brown RL, Vitcenda M, Einerson J, McBride PE. Lower extremity peripheral arterial disease in hospitalised patients with coronary artery disease. *Vasc Med* 2003; 8: 233-236
- Klop RBJ, Eikelboom BC, Taks ACJM. Screening of the internal carotid arteries in patients with peripheral vascular disease by colour-flow Duplex scanning. *Eur J Vasc Surg* 1991;5:41-5
- Hankey GJ, Slaterry JM, Warlow CP. Transient ischaemic attacks. Which patients are at high (and low) risk of serious vascular events? *J Neurol Neurosurg Psychiatr* 1992;55:6540-6552
- Warlow C. The epidemiology of cerebrovascular disease. In: Tooke JE, Lowe GDO (eds). A textbook of vascular medicine. London: Arnold, 1996; 385-400
- Lowe GDO, Rumley A, Tooke JE. Clinical pathophysiology of arterial disease. In: Tooke JE, Lowe GDO (eds). A textbook of vascular medicine. London: Arnold, 1996; 43-59
- Gordon T, Kannel WB. Preposition to atherosclerosis in the head, heart and legs. The Framingham Study. *JAMA* 1972;221:661-666
- Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol* 1999;19: 538-45
- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1339
- Coull AJ, Rothwell PM. What proportion of all acute vascular events in the population are cerebrovascular? Implications for funding of clinical services and research. *Cerebrovasc Dis* 2004;17:21
- Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular study). *Lancet* 2004; 363:1925-1933
- Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness and treatment in primary care. *JAMA* 2001;286:1317-24
- Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for the primary prevention of cardiovascular disease and stroke: 2002 update. Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation* 2002;106:388-391
- Fowkes FGR. Epidemiology of peripheral arterial disease. In Tooke JE, Lowe GDO (eds). A textbook of vascular medicine. London: Arnold 1996; 149-161
- Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet* 1999;353:89-92

- 18 Lawlor DA, Ebrahim S, Davey Smith G. Sex matters: secular and geographical trends in sex differences in coronary heart disease mortality. *BMJ* 2001;323:541-545
- 19 Gray LJ, Bath PMW. The effect of hormone replacement therapy on stroke risk, type and outcome: a systematic review of data from randomised controlled trials. *Cerebrovasc Dis* 2004; 17:18
- 20 Emberson JR, Whincup PH, Morris RW, Walker M. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. *Europ Heart J* 2003; 24:1719-1726
- 21 Dormandy JA, Ray S. The natural history of peripheral arterial disease. In Tooke JE, Lowe GDO (eds). *A textbook of vascular medicine*. London: Arnold 1996;162-175
- 22 Burns P, Gough S, Bradbury AW. Management of peripheral arterial disease in primary care. *BMJ* 2003;326:584-588
- 23 Murray CJL, Lauer JA, Hutuberscy RCW, et al. Effectiveness and costs of interventions to lower systolic blood pressure: a global and regional analysis on reduction of cardiovascular risk. *Lancet* 2003;361:717-725
- 24 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; 326:1419
- 25 Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342:145-53
- 26 Heart Protection Study Collaborative Group. MRC / BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22
- 27 Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363:757-767
- 28 Housley E. Exercise. In: Fowkes FGR (ed). *Epidemiology of peripheral vascular disease*. London: Springer-Verlag 1991;227-34
- 29 Wannamethee G, Shaper AG. Physical activity and stroke in British middle-aged men. *BMJ* 1992; 304:597-601
- 30 Hill J. Physical activity and obesity. *Lancet* 2004; 363:182
- 31 Lowe GDO, Danesh J, eds. Classical and emerging risk factors for cardiovascular disease. *Semin Vasc Med* 2002; 2:229-445
- 32 Homocysteine Studies Collaboration. Homocysteine and risk of ischaemic heart disease and stroke. A meta-analysis. *JAMA* 2002;288:2015-2022
- 33 Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, Schouter EG and the MTHFR Studies Collaboration Group. MTHFR 677C-T polymorphism and risk of coronary heart disease. A meta-analysis. *JAMA* 2002;288:2023-2031
- 34 Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang C-H, Stamfer M. Lowering homocysteine in patients with ischaemic stroke to prevent recurrent stroke, myocardial infarction, and death. *JAMA* 2004; 291:565-575
- 35 Fibrinogen Studies Collaboration. Collaborative meta-analysis of prospective observational studies of plasma fibrinogen and cardiovascular disease. *Europ J Cardiovasc Prev Rehab* 2004; 11:9-19
- 36 Smith FB, Lee AJ, Hau C, Fowkes FGR, Lowe GDO, Rumley A. Plasma fibrinogen, haemostatic factors and prediction of peripheral arterial disease in the Edinburgh Artery Study. *Blood Coagul Fibrinolys* 2000;11:43-50
- 37 Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GDO, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *New Engl J Med* 2004; 350:1387-1397
- 38 Kim RJ, Becker RC. Association between factor V Leiden, prothrombin mutation G20120A, and MTHFR C677T mutations and events of the arterial circulatory system. A meta-analysis of published studies. *Am Heart J* 2003;146:948-957
- 39 Antithrombotic Trialists' Collaboration. Prevention of death, myocardial infarction and stroke by antiplatelet therapy: collaborative meta-analysis of 266 trials involving 200000 patients at high risk of occlusive vascular death. *Br Med J* 2002;325:71-86
- 40 The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502
- 41 Mehta SR, Yusuf S, Peters RJG, et al. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-533
- 42 ESPS-2 Group. European stroke prevention study. 2. Efficacy and safety data. *J Neurol Sci* 1997;151:S1-S77