OCTOBER 2001 volume VI, issue 8

CARDIOLOGY Rounds™

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Novel risk factors for coronary artery disease

BY SALEEM KASSAM, MD, AND DUNCAN STEWART, MD

With the rise in the prevalence of coronary artery disease (CAD), predicting and modifying the risks associated with CAD have gained importance in modern medicine. Large cohort studies have quantified the relative risks attributable to various disease states. Risk-prediction algorithms, such as the Framingham risk table, estimate CAD event rates relative to a reference population.[1] A recent paper suggests the following classification framework (Figure 1).[2]

- **Major independent risk factors** are cigarette smoking, diabetes mellitus, elevated serum total cholesterol, low HDL cholesterol, hypertension, and advancing age.
- **Predisposing factors** have a negative impact on independent risks, and include obesity, abdominal obesity, physical inactivity, a family history of premature CAD, ethnic characteristics, and psychosocial factors.
- **Conditional factors** are associated with risks for CAD, although they may or may not be independently associated. These include elevated serum triglycerides (TG), small LDL particles, lipoprotein(a) [Lp(a)], serum homocysteine (HCY), prothrombotic factors (such as fibrinogen), and markers of inflammation.

A few problems, however, arise with this schema. It has been observed that approximately 50% of all myocardial infarctions (MIs) occur in individuals without hyperlipidemia.[3] Also, an estimated one-third of infarct survivors have no identifiable risk factors. This issue of *Cardiology Rounds* will review some of the novel risk factors associated with the development of CAD and their impact in relation to our traditional understanding of risk.

Pathophysiology of atherosclerosis and plaque rupture

The development of atherosclerotic plaque is a complex process. It predates symptomatic CAD by many years and involves a number of systemic responses.[4] Following the accumulation of lipoprotein particles in the intima, oxidative stress promotes cytokine release and the attraction of inflammatory cells that scavenge the lipids and become foam cells. Further cell signalling mediates the release of effectors, such as matrix metalloproteinases, and the migration of smooth muscle cells from the media to the intima. Subsequent elaboration of extracellular matrix, calcification and fibrosis occur, resulting in a relatively acellular fibrous capsule surrounding a lipid-rich core. Plaque rupture and subsequent thrombosis is related to a number of characteristics, including lesion size and consistency, shear stresses, endothelial function, and degree of inflammation.[5]

Impaired fibrinolysis and thrombosis

PAI-1 and TPA

Thrombus formation at the site of plaque rupture is controlled through the natural fibrinolytic system. The balance between fibrin formation and breakdown is complex, tightly regulated, and may explain differences in the degree and consequences of plaque rupture in CAD events. The two principle inhibitors of fibrinolysis are plasminogen activator inhibitor-1 (PAI-1), and α2-antiplasmin. PAI-1 antagonizes the fibrinolytic activity of circulating and fibrin-bound tissue plasminogen activator (TPA). Several observations have suggested a link between fibrinolytic factors and coronary events.[6] It has been shown that PAI-1 elevation occurs in normoglycemic patients with high levels of insulin

St. Michael's Hospital
30 Bond St.,
Room 9-004, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5330

The opinions expressed are only those of the Divisional members. This publication is made possible through unrestricted grants.

SMH
ST. MICHAEL'S HOSPITAL

UNIVERSITY OF TORONTO

Figure 1: Risk factors for CAD[1]

Major	Predisposing
• Cigarette smoking	• Obesity*†
• Elevated blood pressure	• Abdominal obesity†
• Elevated serum total cholesterol (and LDL-C)	• Physical inactivity*
• Low serum HDL-C	• Family history of premature CHD
• Diabetes mellitus	• Ethnic characteristics
• Advancing age	• Psychosocial factors

Conditional

- Elevated serum triglycerides
- Small LDL particles
- Elevated serum homocysteine
- Elevated serum lipoprotein(a)
- Prothrombotic factors (eg. fibrinogen)
- Inflammatory markers (eg. C-reactive protein)

* Those risk factors are defined as major risk factors by the Framingham Heart Study and the AHA.

† Body weights are currently defined according to body mass index as follows: normal weight, 18.5-24.9 kg/m²; overweight, 25-29 kg/m²; obesity, >30.0 kg/m² (obesity class I, 30.0-34.9; class II, 35.9-39.9; class III, ≥50 kg/m²). Abdominal obesity is defined according to waist circumference; men >102 cm (40 in.) and women >88 cm (35 in.).

(the insulin resistance syndrome [IRS]) and in those with type 2 diabetes mellitus (DM), an association possibly mediated through elevations in triglycerides (TG).[7] PAI-1 levels are lower in premenopausal women and those on hormone replacement therapy; they are increased by angiotensin II, but diminished by ACE-inhibition.

Clinical observations have linked high PAI-1 levels with first MI and the progression of CAD in patients under 45 yrs, as well as the progression to MI in patients with unstable angina and a greater CAD burden.[8-10] Conversely, low PAI-1 levels are thought to be protective. A value that is 1 standard deviation above the mean for plasma fibrinolytic activity predicted 40% fewer CAD events in one study.[11] In a prospective cohort of 3000 patients with angina, followed for 2 years, levels of PAI-1 activity and TPA antigen were significantly higher among those with events, compared to those without events (death/non-fatal MI).[12] The usefulness of PAI-1 as a predictor of future events is seriously impaired by a number of issues.

- Such tests are very difficult to measure, requiring precise phlebotomy techniques and displaying a wide circadian variation, (ie, higher levels in the early morning).[13]
- Associations are confounded by the presence of the IRS, with most of the variation in PAI-1 activity and TPA antigen linked to metabolic parameters (TG, body mass index [BMI], insulin level), rather than variations in PAI-1 gene.[7,14]

Lipoprotein (a)

Lipoprotein(a) [Lp(a)] is a small molecule, consisting of an LDL particle and an apo B-100 component attached to an apo(a) protein that competes with plasminogen for coagulation binding sites. It may, therefore, be thrombogenic and a potential marker for CAD events.[15] In the Framingham cohort, elevated Lp(a) was associated with a significant difference in time to first event over the 16-year follow-up. After adjustments for age, smoking status, glucose intolerance, hypertension (HTN), BMI, and major lipid abnormalities, the presence of Lp(a) increased the relative risk for MI, angina pectoris, and all CAD events to 1.9, 2.2, and 1.9, respectively. Such observations have been corroborated in several large, prospective studies.[17-19]

Other investigators, however, have made contradictory observations.[20-22] In the Physicians Health Study, apparently healthy men aged 40-84 years, were followed for a mean of 5 years, without a correlation between Lp(a) and coronary events. Also, Lp(a) is tightly linked to other risks for CAD (ie, LDL, HDL, smoking), and exhibits a wide variation across ethnic groups (African-Americans and South Asians have higher levels).[3] There has been no standardization of measurements, outcome events, or populations between studies, and analyses of all prospective data suggest that any association in a general population between Lp(a) and events, is of a modest degree.[3] Therefore, from a population screening-based perspective, little weight can currently be assigned to Lp(a) as a marker of CAD events.

Homocysteine

Homocysteine (HCY) is an intermediate formed during the metabolism of methionine, an essential amino acid (Figure 2).[23] Serum levels are dependent on various enzymes (including cystathionine beta-synthetase, and methyltetrahydrofolate reductase), and co-factors, such as folate, Vitamin B_6 and B_{12}.[23,24] Several studies have suggested that the HCY median value for an adult male is 10 µmol/L.[25] Correlates of elevated serum HCY include: increasing age, male gender, alcohol use, smoking, renal impairment, hypothyroidism, systemic lupus erythematosus, transplantation, corticosteroids, and cyclosporine. Inherited hyperhomocystinemia manifests as premature, severe atherosclerosis.[26,27] Although the mechanism for accelerated atherosclerosis is not clear, proposed mechanisms for increased risk of CAD have included: endothelial toxicity, an induction of vascular smooth muscle proliferation, impairment of nitric oxide, and increased LDL oxidation.

In a meta-analysis of predominantly case-controlled studies, 14 of 17 papers supported the link between elevated HCY

Figure 2: Formation of homocysteine in methionine metabolism[23]

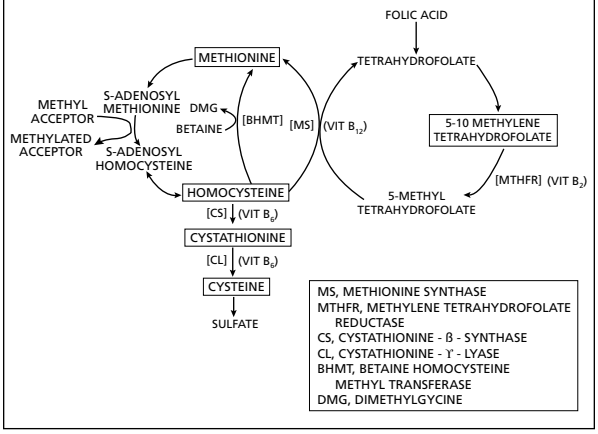
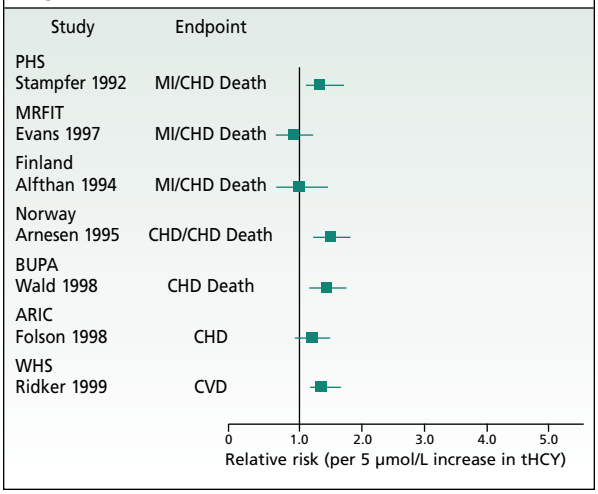


Figure 3: Relative risk for incremental HCY[3]



and an increased risk for vascular disease.[28] Furthermore, folic acid supplementation lowers HCY and was associated with lower events among patients with elevated HCY.[29] From a population-based perspective, it is estimated that 400 µmol per day of folic acid (if 50% effective), would result in a mean 6 µmol/L decrease in the population's HCY, and an absolute 4.4% decrease in CHD death.[28] Prospective studies, however, reveal a much more modest relationship, with a pooled estimate of relative risk for each 5 µmol/L increment in HCY, of less than 1.5 (Figure 3).[3]

The uncertainty in the strength of an association linking HCY with CAD events can be accounted for on several levels. Most retrospective studies involved patients with competing risks for CAD events, and since HCY levels increase after MI and stroke, it makes case-control studies less useful. As with Lp(a), the correlation with vascular events may only be valid at very high levels of HCY, representing a small segment of the population. An increase in folic acid supplementation of 100 µmol daily in breads and cereals has been underway in the US since 1997. It has yielded a 10% fall in mean population HCY levels and a 50% drop in those with modestly elevated HCY levels, such that, currently, low folic acid levels are found in <1% of the population.[30,31] Finally, no treatment strategy has been appropriately evaluated.

Despite these reservations, it has been suggested that screening may be reasonable in high-risk individuals and those with a strong family history for premature atherosclerosis or other arterial occlusive diseases, particularly in the absence of other risk factors.[23] Furthermore, in patients with a basal homocysteine level of >10 µmol/L, an unproven strategy includes dietary supplementation and/or a combination of vitamins B_6, B_{12} and folic acid.

Other hemostatic factors

Factor VII, fibrinogen

Several prospective studies address the relationship between coagulation factors and the risk of CAD events. The Northwick Park Study followed 1511 healthy, white male patients, aged 40-64 yrs, for 5 years.[11] The cardiovascular event risk associated with an elevation of 1 standard deviation (SD), was 62%, 84%, and 43% for factor VII, fibrinogen, and total cholesterol (TC), respectively. Importantly, after correcting for baseline imbalances, the association between a future CAD event and TC was not significant, making the conclusions of this small study less reliable.

The Prospective Cardiovascular Munster Study (PROCAM) tracked a cohort of 10,000 healthy German employees for 8 years.[32] The mean age at entry was 49 yrs and 2780 men had prospective measurements of fibrinogen and factor VII. In univariate analysis, association between baseline elevations in fibrinogen and a recurrent event was strong (P<.001), while that for factor VII was weak (P=.023). Furthermore, factor VII added little to risk beyond LDL-cholesterol.

The Atherosclerosis Risk in Communities (ARIC) study involved 14,477 healthy patients, aged 45 to 64 years, from 3 counties in the United States.[33] Following baseline coagulation measurements, the cohort was prospectively followed for CAD death or non-fatal MI over 4-7 years. Future risk correlated with initial levels of fibrinogen, von Willebrand factor, and leukocyte count. Age-race and centre-adjusted relative risk was significantly higher between the lowest and highest tertiles of fibrinogen (2.77 for men, 2.67 for women). When adjusted for smoking, hypertension, DM, and physical inactivity, only fibrinogen was independently associated with a CAD event and death.

Many mechanisms may account for the association between elevated fibrinogen and CAD events.[34,35] Fibrin binds to LDL particles, stimulates smooth muscle proliferation, and is scavenged by foam cells. It is a protein of large molecular weight, which may increase blood coagulability through increased blood viscosity. Fibrinogen is cross-linked at the platelet GP IIb/IIIa receptor site, promoting aggregation and the propagation of larger fibrin clots that may be more difficult to lyse. Apart from its properties as an acute phase reactant, fibrinogen levels rise over time in many health conditions, particularly in the presence of many CAD risk factors (ie, age, heredity, smoking, obesity, hypertension, hypercholesterolemia and hypertriglyceridemia, DM, pregnancy, menopause, and estrogen replacement therapy). Conversely, levels fall with exercise and moderate alcohol consumption. A meta-analysis of studies examining the relationship to CAD, reported a risk ratio of 1.8 for CAD events between upper and lower tertiles of fibrinogen (95% CI, 1.6-2.0).[36]

Unfortunately, the usefulness of fibrinogen as a risk factor is limited by confounding associations with recognized risks for CAD, and a lack of agreement or standardization regarding fibrinogen measurement. More recent measurement techniques have yielded more promising results.[37] Although agents that reduce fibrinogen levels are unknown, treatment strategies have not strengthened the confidence in its association with CAD risk. For example, a recent trial of fibrate therapy failed to show a reduction in vascular events, despite a 9% reduction in fibrinogen.[38]

Inflammatory markers

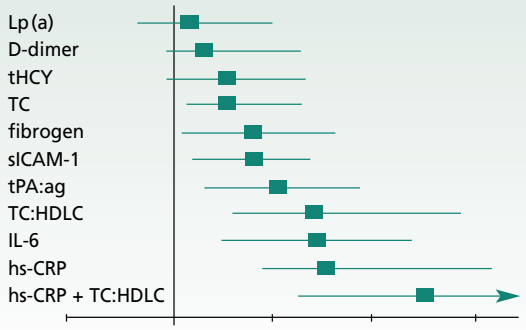
C-reactive protein

Inflammation plays a role in all phases of atherosclerosis, including plaque rupture and thrombosis.[39] Although their role in the development of atherosclerotic pathology is still unclear, it has been shown that adhesion molecules (eg, intracellular and vascular adhesion molecules, ICAM-1, VCAM) allow monocyte attachment to endothelium.[3,40] Both interleukin-6 (IL-6) and tumour necrosis factor (TNF) are potent cytokines. C-reactive protein (CRP) activates complement, and is associated with increased tissue factor expression. It is up-regulated when foam cells are unable to digest lipid (Stewart DJ, Personal communication, 2001).[41] Serum amyloid-A binds HDL particles in serum and fibrinogen participates in coagulation. Recently, well-conducted prospective studies have shown that inflammation precedes the development of clinical disease and may serve as a marker for future events.[42,43]

CRP may be the most useful marker of inflammation associated with CAD. In the absence of acute injury (where it rises approximately 100-fold), it serves as a marker for low-grade, chronic inflammation.[44] In contrast to fibrinogen, CRP levels rise following hormone replacement therapy, suggesting a different mechanism. Levels also increase with smoking, however, several studies have shown CRP to hold prognostic value in the acute coronary syndromes, acute MI, and following coronary angioplasty.[45-49] Two studies suggest that CRP levels may also reflect the burden of atherosclerotic disease, both in the coronary and peripheral arterial circulation.[50,51]

The Physicians Health Study provides important insight into the link between CRP and CAD.[52] Baseline levels of CRP were measured in 543 healthy MDs (no CAD, chronic illness, or cancer), and compared with an equal number of controls matched for age, smoking status, and time of follow-up (mean = 8 yrs) for CHD event (future MI). This was done in the context of a randomized trial of ASA and beta-carotene as primary prevention of a CAD event. CRP was highly predictive for future events after adjustments for other CAD risks, including BMI, DM, HTN, family history, total cholesterol, HDL, TG, Lp(a), TPA antigen, fibrinogen, and HCY. The correlation was graded, based on the level of CRP, with relative risks from 1.0 to 2.6 for highest quartile CRP (>2.11, $P<.001$). Similar results were found among women.[53] The association between baseline CRP and subsequent events was maintained over 6 years of follow-up, with a relative risk of 1.5 for each quartile change in CRP. Importantly, this risk was found to add predictive value to total cholesterol (Figure 4).[54] A meta-analysis of prospective studies, the majority adjusted for age, sex, and smoking, revealed a relative risk of 1.7 between the top third and bottom third of CRP (95% CI, 0.4-2.1).[36]

Figure 4: Relative risk of MI based on CRP in addition to other risk factors[3]



hs-CRP = High-sensitivity C-reactive protein

Furthermore, there is evidence that treatment may modify risk. In the US Physicians Health Study, a graded response to ASA (325 mg/alternate days) was observed. The attributable risk reduction for future MI with aspirin was 13% among those with the lowest baseline CRP, and 55% among those with the highest values (Figure 5).[3,52] Data from the Cholesterol and Recurrent Events (CARE) trial, reveal an interaction between HMG-CoA reductase inhibitors, inflammation, and subsequent events.[55] Among patients with average cholesterol values, pravastatin treatment significantly lowered CRP levels among those with and without overt evidence of CAD.[56]

In evaluating the evidence supporting novel risks for CAD, Ridker and colleagues propose that the following:

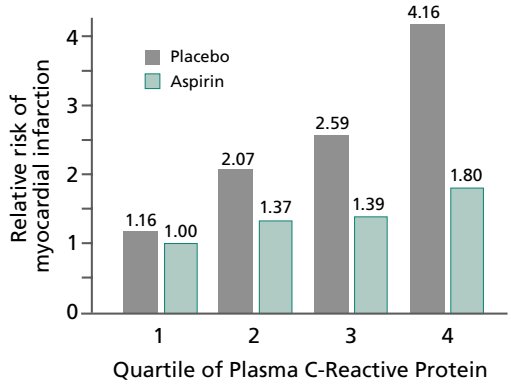
- Studies should use standardized assay conditions.
- Studies should demonstrate a consistent effect in prospective cohorts.
- Study markers should be additive to TC and HDL.

Currently, only CRP meets these criteria. Among novel risk factors for CAD events, CRP may prove to be stronger than, and additive to, total cholesterol in predicting future events.[3,42]

Cautionary points in interpreting novel risk factors

Several points must be emphasized in any comparison of risk factors for CAD. The level of evidence supporting an association must be considered. Cross-sectional studies and case-control studies suffer from an ascertainment bias, making it difficult to determine the sequence of events and the appearance of the marker or the disease in question. While cohort studies overcome this, they cannot control for imbalances in the distribution of factors associated with the disease in question. Even among the largest population-based studies, special groups – such as those with renal insufficiency and co-morbid disease – are generally under-represented. The findings of large studies do not adequately capture all demographic groups of importance, such as ethnic

Figure 5: Risk reduction by aspirin relative to baseline CRP[52]



groups and women, that may differ significantly in baseline risk, thus limiting the applicability of their conclusions. Finally, treatment trials strengthen the causal relationships between factors and disease; however, they are not available for any novel risk markers.

Traditional risk estimates are linked to rates of events that change as newer treatment modalities become available. Also, population-based risk estimates are less accurate at the extremes of baseline risk. Most risk estimates apply to a limited period of time. The Framingham study, one of the largest and longest of its kind, provides risk estimates for 10 years, therefore, lifetime risk estimates for younger individuals require extrapolation.[1] Risk estimates for newer markers are of a substantially shorter time frame. In addition, the value of employing such risk markers, in the absence of effective treatment, can be questioned.

Summary

While traditional risk factors provide an estimate of CAD risk, their predictive value is limited. Novel factors address various aspects of atherogenic development, but most are linked to traditional parameters. New, inflammatory markers, particularly CRP, may have additive, independent prognostic value; however, the mechanism that relates their presence to CAD events is not clear. Once a mechanistic relationship is established, treatment trials may have value in attempting to modify the disease state.

References

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97(18):1837-1847.
2. Fuster V, Gotto AM, Jr. Risk reduction. *Circulation* 2000;102(20, Suppl 4):IV94-IV102.
3. Ridker PM. Novel risk factors and markers for coronary disease. *Adv Intern Med* 2000;45:391-418.
4. Libby P. Novel atherosclerotic risk factors. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 6th ed. Philadelphia, PA: Saunders;2001:1026-1033.
5. Kaplan NM. The vascular biology of atherosclerosis. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA: Saunders;2001:1002-1004.
6. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med* 2000;342(24):1792-1801.
7. Juhan-Vague I, Thompson SG, Jespersen J. Involvement of the hemostatic system in the insulin resistance syndrome. A study of 1500 patients with angina pectoris. The ECAT Angina Pectoris Study Group. *Arterioscler Thromb* 1993;13(12):1865-1873.
8. Thogersen AM, Jansson JH, Boman K, et al. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation* 1998; 98(21):2241-2247.
9. Held C, Hjemdahl P, Rehnqvist N, et al. Fibrinolytic variables and cardiovascular prognosis in patients with stable angina pectoris treated with verapamil or metoprolol. Results from the Angina Prognosis study in Stockholm. *Circulation* 1997; 95(10):2380-2386.
10. Bavenholm P, de Faire U, Landou C, et al. Progression of coronary artery disease in young male post-infarction patients is linked to disturbances of carbohydrate and lipoprotein metabolism and to impaired fibrinolytic function. *Eur Heart J* 1998;19(3):402-410.
11. Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 1986;2(8506):533-537.
12. Juhan-Vague I, Pyke SD, Alessi MC, Jespersen J, Haverkate F, Thompson SG. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. ECAT Study Group. European Concerted Action on Thrombosis and Disabilities. *Circulation* 1996;94(9):2057-2063.
13. Angleton P, Chandler WL, Schmer G. Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1). *Circulation* 1989;79(1):101-106.
14. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 1996;334(15):952-957.
15. Loscalzo J. Lipoprotein(a). A unique risk factor for atherothrombotic disease. *Arteriosclerosis* 1990;10(5):672-679.
16. Bostom AG, Cupples LA, Jenner JL, et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *JAMA* 1996;276(7):544-548.
17. Cremer P, Nagel D, Labrot B, et al. Lipoprotein Lp(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and other risk factors: results from the prospective Gottingen Risk Incidence and Prevalence Study (GRIPS). *Eur J Clin Invest* 1994; 24(7):444-453.
18. Wald NJ, Law M, Watt HC, et al. Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994;343(8889):75-79.
19. Wild SH, Fortmann SP, Marcovina SM. A prospective case-control study of lipoprotein(a) levels and apo(a) size and risk of coronary heart disease in Stanford Five-City Project participants. *Arterioscler Thromb Vasc Biol* 1997;17(2):239-245.
20. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA* 1993; 270(18):2195-2199.
21. Cantin B, Gagnon F, Moorjani S, et al. Is lipoprotein(a) an independent risk factor for ischemic heart disease in men? The Quebec Cardiovascular Study. *J Am Coll Cardiol* 1998;31(3):519-525.
22. Jauhiainen M, Koskinen P, Ehnholm C et al. Lipoprotein(a) and coronary heart disease risk: A nested case-control study of the Helsinki Heart Study participants. *Arteriosclerosis* 1991;89:59-67.
23. Malinow MR, Bostom AG, Krauss RM. Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation* 1999;99(1): 178-182.

24. Miner SE, Cole DE, Stewart DJ. Homocysteine and vascular disease. Vol 1, Issue 5, 1996.
25. Robinson K, Gupta A, Dennis V, et al. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. *Circulation* 1996;94(11):2743-2748.
26. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol* 1969;56(1):111-128.
27. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Engl J Med* 1998;338(15):1042-1050.
28. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995;274(13):1049-1057.
29. Ubbink JB, van der MA, Vermaak WJ, Delport R. Hyperhomocysteinemia and the response to vitamin supplementation. *Clin Investig* 1993;71(12):993-998.
30. Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med* 1999;340(19):1449-1454.
31. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998;316(7135):894-898.
32. Heinrich J, Balleisen L, Schulte H, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. *Arterioscler Thromb* 1994;14(1):54-59.
33. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 1997;96(4):1102-1108.
34. Montalescot G, Collet JP, Choussat R, Thomas D. Fibrinogen as a risk factor for coronary heart disease. *Eur Heart J* 1998;19 (Suppl H):H11-H17.
35. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. *Ann Intern Med* 1993;118(12):956-963.
36. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998;279(18):1477-1482.
37. Stec JJ, Silbershatz H, Tofler GH, et al. Association of fibrinogen with cardiovascular risk factors and cardiovascular disease in the Framingham Offspring Population. *Circulation* 2000;102(14):1634-1638.
38. Behar S. Lowering fibrinogen levels: clinical update. BIP Study Group. Bezafibrate Infarction Prevention. *Blood Coagul Fibrinolysis* 1999;10 (Suppl 1): S41-S43.
39. Ross R. Atherosclerosis is an inflammatory disease. *Am Heart J* 1999;138(5 Pt 2):S419-S420.
40. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91(11):2844-2850.
41. Stewart DJ. Personal Communication, 2001.
42. Libby P, Ridker PM. Novel inflammatory markers of coronary risk: theory versus practice. *Circulation* 1999;100(11):1148-1150.
43. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342(12):836-843.
44. Weatherall DJ, Ledingham JGG, Warrell DA, eds. The acute phase response and c-reactive protein. In: *Oxford Textbook of Medicine*, 3rd ed. Oxford, England: Oxford University Press;1996.
45. Azar RR, McKay RG, Kiernan FJ, et al. Coronary angioplasty induces a systemic inflammatory response. *Am J Cardiol* 1997;80(11):1476-1478.
46. Klinkhardt U, Kirchmaier CM, Westrup D, et al. Ex vivo—in vitro interaction between aspirin, clopidogrel, and the glycoprotein IIb/IIIa inhibitors, abciximab and SR121566A. *Clin Pharmacol Ther* 2000;67(3):305-313.
47. Tomoda H, Aoki N. Prognostic value of C-reactive protein levels within six hours after the onset of acute myocardial infarction. *Am Heart J* 2000; 140(2):324-328.
48. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 1997;349(9050):462-466.
49. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol* 1998;31(7):1460-1465.
50. Torzewski J, Torzewski M, Bowyer DE, et al. C-reactive protein frequently colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions of human coronary arteries. *Arterioscler Thromb Vasc Biol* 1998;18(9):1386-1392.
51. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998;97(5):425-428.
52. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336(14):973-979.
53. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98(8):731-733.
54. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97(20):2007-2011.
55. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998;98(9):839-844.
56. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; 286(1):64-70.

Upcoming Scientific Meetings

11-14 November, 2001
American Heart Association Scientific Sessions
Anaheim, California
CONTACT: AHA National Centre, Dallas Texas
Phone: (214) 706-1543
Fax: (214) 706-5262
Email: sessions@heart.org

Media registration email: sessionsmedia@heart.org

06-08 December, 2001
The 32nd Annual Heart & Stroke Clinical Update
Toronto, Ontario
CONTACT: Dawn Murphy
Phone: 416-489-7111, ext. 453
Fax: 416-489-7003
Email: dmurphy@hsf.on.ca

25-27 January, 2002
The 21st Annual Perspectives on New Diagnostic and Therapeutic Techniques in Clinical Cardiology
Lake Buena Vista, Florida
CONTACT: Phone: 301-897-5400, ext. 694
Fax: 301-897-9745
Email: resource@acc.org

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.