Cardiovascular disease: major journals

Statin-mediated anti-inflammatory effects may contribute to the ability of statins to reduce risk for cardiovascular disease

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It has been proposed that statins reduce cardiovascular events to a larger extent than explicable by their effects on lipid levels. Consequently, studies have attempted to address the effects of statins on non-lipid serum markers, and to correlate these changes with cardiovascular outcomes.

This article by Balk et al represents a systematic review, from a Medline search from 1980–2003, excluding studies of cerivastatin, drug combinations and patients with organ transplants.

The review demonstrates that all statins are equally effective at lowering C-reactive protein levels, without a dose-dependent effect. No correlation has been demonstrated between the effect of statins on C-reactive protein level and cardiovascular outcomes. It appears that statins do not affect fibrinogen levels. No effect has been shown for statins on levels of homocystine, low-density lipoprotein cholesterol oxidation, tissue plasminogen activator or plasminogen activator inhibitor. Likewise, there is no conclusive data on platelet aggregation.

Of the non-lipid markers associated with cardiovascular disease that were studied, statins do reduce C-reactive protein level, which may contribute to the reduction of cardiovascular risk. However, data on these effects on non-lipid serum markers are insufficient for clinical extrapolation in relation to individual patients or specific statins.

LANCET

Metformin review generates correspondence

Readability	✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 McKenzie and Wilcox refer to a review by Krum and Gilbert (2003), which contraindicated metformin in patients with chronic heart failure.

2 Metformin is a commonly used anti-hyperglycaemic agent, which improves insulin sensitivity, decreases hepatic glucose production and slightly reduces intestinal absorption of glucose. It is used with increasing frequency, especially in obese patients with type 2 diabetes, in whom it reduces cardiovascular mortality and morbidity.

3 Type 2 diabetes, obesity and insulin resistance are often seen in patients with chronic heart failure. Metformin promotes weight loss and has beneficial effects on several other cardiovascular risk factors.

4 The corresponders agree that metformin should be avoided or discontinued in patients with decompensated or unstable heart failure, but advocate that metformin be continued to treat patients with diabetes with stable chronic heart failure and normal renal function.

5 Sosin et al also refer to Krum and Gilbert's (2003) article, which summarises succinctly the effect of African-American ethnicity in heart failure. They state, however, that other ethnic groups should not be ignored.

6 Patients of South Asian, as well as African Caribbean or African American, origin could bear a greater burden of disease as a result of their development of heart failure at a younger age. Trials in heart failure should, therefore, address the population at risk and examine mechanisms for the ethnic disparities seen.

Krum H, Gilbert RE (2003) Demographics and concomitant disorders in heart failure. Lancet **362**: 147–58

McKenzie DB, Wilcox RG (2003) Heart failure: treatment and ethnic origin (correspondence). Lancet **362**: 919

Sosin MD, Bhatia GS, Davis RC, Connolly DL, Lip GYH (2003) Heart failure: treatment and ethnic origin (correspondence). *Lancet* **362**: 919–20

ANNALS OF INTERNAL MEDICINE

Effects of statins on non-lipid serum markers in CVD

Readability	✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 Statins reduce risk for cardiovascular disease (CVD) to a greater extent than can be explained by their effect on lipids.

2 The purpose of this study was to summarise the effects of statins on non-lipid serum markers and to correlate the effect of statins on serum markers with lipid levels and cardiovascular outcomes.

3 A Medline search (from 1980–2003) collected studies reporting original data in at least 10 patients on the effect of statins on outcomes of interest. Studies of cerivastatin, of drug combinations, of fewer than 10 patients, and of patients with organ transplants were excluded. Where appropriate, meta-analyses were performed.

4 All statins are effective at lowering C-reactive protein levels, and the effect is not dose-dependent. The studies do not show a correlation between the effects of statins on C-reactive protein levels and on lipids or cardiovascular outcomes.

5 Statins do not affect fibrinogen levels, and have little effect on lipid oxidation, tissue plasminogen activator or plasminogen activator inhibitor.

6 Findings suggest that statin-mediated anti-inflammatory effects may contribute to the ability of statins to reduce risk for cardiovascular disease.

7 Overall, however, available data are insufficient to support recommendations for using non-lipid serum markers in decisions regarding statin therapy for individual patients.

Balk EM, Lau J, Goudas LC et al (2003) Effects of statins on non-lipid serum markers associated with cardiovascular disease. *Annals of Internal Medicine* **139**: 670–82

JOURNAL OF INTERNAL MEDICINE

Metformin increases homocysteine levels

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Homocysteine is an independent and potentially modifiable risk factor that may be strongly linked to cardiovascular prognosis in type 2 diabetes.

2 Low serum folate and vitamin B12 levels are strongly associated with increased serum homocysteine. Serum vitamin B12 level is known to decrease during metformin treatment, hence it is postulated that treatment with metformin might increase homocysteine levels.

3 In this randomised placebo-controlled trial of 745 patients with insulin-treated type 2 diabetes, the effects of 16 weeks of treatment with metformin on levels of homocysteine, folate and vitamin B12 was assessed.

4 Metformin use was associated with an increase in homocysteine of 4% and with decreases in folate (-7%) and vitamin B12 (-14%) compared with placebo.

5 In addition, the increase in serum homocysteine was mediated by the decreases in serum folate and vitamin B12.

6 These data suggest that the known favourable effects of metformin may be even more pronounced if decreases in folate and vitamin B12 are avoided.

7 It is not clear whether these results can be generalised to patients with type 2 diabetes who are not treated with insulin.

8 The clinical significance of these findings is unclear and needs further investigation.

Wulffele MG, Kooy A, Lehert P (2003) Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized placebo-controlled trial. Journal of Internal Medicine **254**: 455–63

ARCHIVES OF INTERNAL MEDICINE

Vascular disease and longevity

Readability	✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 To determine the likelihood of maintaining intact health and functioning, 2932 men and women aged ≥65 years were followed up for 8 years.

2 'Successful aging' was defined as remaining free of cardiovascular disease, cancer and chronic obstructive pulmonary disease and with intact physical and cognitive functioning.

3 Younger age and a lower extent of subclinical cardiovascular disease were independently associated with successful aging.

4 There is a graded relationship between the extent of vascular disease measured non-invasively and the likelihood of maintaining intact health and function.

5 Prevention of subclinical vascular disease may increase the quality and quantity of years in late life.

Newman AB, Arnold AM, Naydeck BL et al (2003) Successful aging. Effect of subclinical cardiovascular disease. Archives of Internal Medicine **163**: 2315–22

INTERNAL MEDICINE JOURNAL

Glucose-insulin-potassium therapy reviewed

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Glucose-insulin-potassium infusion as a metabolic therapy was first advocated for the management of acute myocardial infarction (AMI) in the 1960s.

2 Enthusiasm for its use has been patchy, although several studies in the mid-1990s revived the interest in the glycometabolic aspects of patients with AMI.

3 Results are conflicting over the significance of the glycometabolic state following acute coronary occlusion and the role of insulin-based infusion therapy.

4 Although most of the available evidence is in favour of an insulin-based approach, there are many aspects of this therapy that require clarification. More evidence is needed before it is adopted in routine clinical practice.

Wong V, Cheung NW, Boyages SC (2003) Glycometabolic status and acute myocardial infarction: has the time come for glucose-insulin-(potassium) therapy? Internal Medicine Journal **33**: 443–49

ARCHIVES OF INTERNAL MEDICINE

High cholesterol levels increase risk of CHD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The study assessed how cholesterol levels at different ages modify the remaining lifetime risk of coronary heart disease (CHD).

2 The study included Framingham Heart Study participants (3269 men and 4019 women) examined from 1971 through 1996 who did not have CHD and were not receiving lipid-lowering therapy.

3 At index ages of 40, 50, 60, 70 and 80 years, patients were stratified by total cholesterol level and subfractions.

4 At each index age, lifetime risk of CHD increased with higher cholesterol levels, and time to event decreased. Lifetime risks contrasted sharply with shorter-term risks.

5 Lifetime risk of CHD increases with higher total cholesterol levels at all ages, supporting a role for cholesterol screening in younger patients.

Lloyd-Jones DM, Wilson PWF, Larson MG et al (2003) Lifetime risk of coronary heart disease by cholesterol levels at selected ages. Archives of Internal Medicine **163**: 1966–72

'There is a graded relationship between the extent of vascular disease measured non-invasively and the likelihood of maintaining intact health and function.'

'Lifetime risk of CHD increases with higher total cholesterol levels at all ages, supporting a role for cholesterol screening in younger patients.'