

## Diabetes journals

### Support provided for use of statins in people without CHD



Mark Kearney,  
Cardiologist,  
King's College  
Hospital, London

**I**t is now well accepted that type 2 diabetes should be considered as a cardiovascular disease. If an outpatient with type 2 diabetes presents to me, I adopt a very low threshold for coronary angiography. However, an important question is what to

do if the outpatient does not have coronary heart disease (CHD).

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a multicentre trial designed to compare two antihypertensive treatment strategies for the prevention of CHD events in 19 342 hypertensive patients without a history of CHD. The ASCOT lipid-lowering arm (see right) evaluated the impact of statin use in patients with type 2 diabetes, controlled hypertension and no documented history of CHD.

In a two-by-two factorial design, ASCOT included a double-blind, randomised comparison of the cardiovascular effects of atorvastatin with placebo among 10 305 patients who had a cholesterol level <6.5 mmol/l. The present report analysed results in 2532 people with diabetes – this was a sub-study that was selected *a priori*.

In total, 1258 people with diabetes were given 10 mg atorvastatin and 1274 were given placebo. The mean number of additional risk factors was about three. At the end of follow-up, patients receiving atorvastatin had cholesterol levels approximately 0.9 mmol/l less than those who were placebo treated. Blood pressure control was excellent throughout the study, at around 138/77 mmHg.

Atorvastatin reduced the total number of cardiovascular events by 23% (hazard ratio, 0.77; 95% confidence interval 0.61–0.98;  $P=0.036$ ). This result was unaffected by baseline cholesterol concentration.

These findings add to those of the Heart Protection Study, in which people with diabetes had higher cholesterol levels and were at higher risk of adverse events. Moreover, the findings of the present study demonstrate that, even in people with diabetes who have a relatively lower risk and have good blood pressure control, the addition of statins improves cardiovascular outcomes. It is becoming clearer that all people with diabetes should probably be on a statin; furthermore, aggressive risk factor reduction, including blood pressure, should be pursued in all people with diabetes and not just those with documented CHD.

### DIABETES CARE



### Atorvastatin reduces CV events in ASCOT sub-group

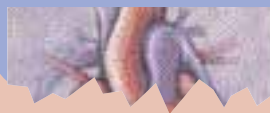
Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

- Of the 10 305 people in the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 2532 had type 2 diabetes at randomisation, and a separate analysis of their results was a prespecified aim of the trial.
- This sub-group had well-controlled hypertension, no established coronary heart disease (CHD) and cholesterol levels that were average or below average.
- Atorvastatin 10 mg/day was given to 1258 individuals, while the other 1274 received placebo.
- After a median follow-up of 3.3 years, total and LDL-cholesterol were both reduced by 0.9 mmol/l in the atorvastatin arm.

- Of the people given atorvastatin, 9.2% had major cardiovascular (CV) events or underwent CV procedures; for those on placebo this figure was 11.9% (hazard ratio, 0.77; 95% confidence interval, 0.61–0.98;  $P=0.036$ ).
- This reduction in the prevalence of major CV events or procedures with atorvastatin equated to around nine individuals per year for every 1000 treated.
- The authors use the results to recommend that all people with type 2 diabetes and hypertension (or at least those who have had diabetes for 10 years or more or are older than 50) be routinely considered for statins.

Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G et al (2005) Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm (ASCOT-LLA). *Diabetes Care* **28**(5): 1151–7

### DIABETOLOGIA



### Sex differences apparent for links between diabetes, MI and mortality

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

- No previous study had looked at the associations of type 2 diabetes and a history of myocardial infarction (MI) with the separate end points of coronary heart disease, stroke, cardiovascular (CV) disease and total mortality.

- Data were analysed from 51 735 Finnish men and women aged 25–74 years over a mean follow-up period of 17.2 years.

- Diabetes and MI were both linked to a marked increase in CV and total mortality.

- In men, the association between MI and mortality was greater than that between diabetes and mortality; for women, the reverse was true.

- A major implication of the findings is that more active management of diabetes may be important in reducing CV and total mortality, especially in women.

Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J (2005) Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. *Diabetologia* **48**(5): 856–61

## DIABETES

### Intensive lifestyle intervention aids non-traditional CV risk factors

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

**1** In the Diabetes Prevention Program, the effect on progression to diabetes of metformin or intensive lifestyle intervention was examined in people with impaired glucose tolerance.

**2** This study (n=3234) addressed the need for a large trial to examine the effect of these interventions on the non-traditional cardiovascular (CV) risk factors of sub-clinical inflammation (indicated by C-reactive protein [CRP]) and impaired coagulation (indicated by fibrinogen).

**3** Fibrinogen levels decreased by 2.0% in the lifestyle group and 0.3% in the metformin group but increased by 0.5% with placebo, from baseline to 1 year.

**4** The result for lifestyle intervention was significant ( $P=0.001$ ) relative to both metformin and placebo.

**5** CRP levels were analysed by sex because of the widely known disparity between women and men.

**6** For women, the median changes in CRP from baseline to 1 year were -29%, -14% and 0% for the lifestyle, metformin and placebo groups, respectively.

**7** For men, the respective results were -33%, -7% and +5%.

**8** The effect of lifestyle intervention was significant ( $P<0.001$ ) relative to both metformin and placebo in men and women.

**9** The results hint that, through its effect on certain non-traditional CV risk factors, lifestyle intervention could reduce the risk of CV disease.

Haffner S, Tempresa M, Crandall J, Fowler S, Goldberg R, Horton E et al (2005) Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes* **54**(5): 1566-72

## DIABETES CARE

### Use of carotid IMT improves CV risk assessment

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

**1** It is recommended by consensus guidelines that cardiovascular (CV) risk assessment be used in the primary prevention of coronary events.

**2** A prospective study of 229 people with type 2 diabetes and at least

one other CV risk factor but no CV complications was carried out to examine if carotid ultrasonography had predictive value.

**3** Carotid intima-media thickness (IMT) was found to independently predict CV events ( $P=0.045$ ), and had a similar predictive value to the Framingham score.

**4** In addition, a combination of these two indices, it is suggested by the authors, further improves the prediction of risk.

Bernard S, Serusclat A, Targe F, Charriere S, Roth O, Beaune J et al (2005) Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. *Diabetes Care* **28**(5): 1158-62

## DIABETES CARE

### Elevated CRP levels seen in children and adolescents with the metabolic syndrome

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

**1** It is known that adults with the metabolic syndrome have elevated C-reactive protein (CRP) levels; this study aimed to see if this finding holds in children and adolescents.

**2** Data were used from the National Health and Nutrition Examination

Survey 1999-2000, with 1366 individuals aged between 12 and 17 years being investigated.

**3** The proportion of people with a CRP level  $>3.0$  mg/l (deemed to place adults at high risk of CV disease) was 38.4% among those with the metabolic syndrome and 10.3% among those without ( $P=0.007$ ).

**4** Waist circumference was the only component of the metabolic syndrome that was found to be independently associated with CRP levels.

**5** It remains to be seen, though, if the elevated CRP levels relate to future adverse health events.

Ford ES, Ajani UA, Mokdad AH. The metabolic syndrome and concentrations of C-reactive protein among U.S. youth. *Diabetes Care* **28**(4): 878-81

## DIABETES CARE

### ATPIII but not WHO metabolic syndrome criteria have prognostic value

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

**1** There is a need for research into the prevalence of the metabolic syndrome in older people, especially given that there two sets of criteria, one from the World Health Organization

(WHO) and the other from the National Cholesterol Education Program Adult Treatment Panel III (ATPIII).

**2** This study found a prevalence of 21.0% for the WHO criteria and a prevalence of 28.1% for the ATPIII criteria in people aged 65 years or older (n=2175) from the Cardiovascular Health Study (concordance was 80.6%).

**3** The metabolic syndrome predicted coronary or cerebrovascular events independently using ATPIII criteria but not WHO criteria.

Scuteri A, Najjar SS, Morrell CH, Lakatta EG (2005) The metabolic syndrome in older individuals: prevalence and prediction of cardiovascular events: the Cardiovascular Health Study. *Diabetes Care* **28**(4): 882-7

**‘The results hint that, through its effect on certain non-traditional CV risk factors, lifestyle intervention could reduce the risk of CV disease.’**

**‘The metabolic syndrome predicted coronary or cerebrovascular events independently using ATPIII criteria but not WHO criteria.’**

## DIABETES CARE



### Energy expenditure affects metabolic syndrome incidence independently of aerobic fitness

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

**1** It was previously unknown whether an objective measure of physical activity energy expenditure (PAEE) could be used, independently of aerobic fitness, to prospectively determine progression to the metabolic syndrome.

**2** Over a period of 5.6 years, 605 middle-aged individuals who were not considered to have the metabolic syndrome were studied.

**3** Linear models were employed to determine the independent prospective associations between PAEE, aerobic fitness ( $VO_{2max}$ ) and progression to the metabolic syndrome.

**4** PAEE was found to have a statistically significant predictive capacity for progression to the metabolic syndrome ( $P=0.046$ ), independently of aerobic fitness, as well as other confounding factors such as body fat.

**5** Aerobic fitness, however, did not have a statistically significant predictive capacity independent of PAEE.

**6** The results suggest that even if improvements in aerobic fitness are absent, physical activity is still an important means of preventing the metabolic syndrome.

Ekelund U, Brage S, Franks PW, Hennings S, Emms S, Wareham NJ (2005) Physical activity energy expenditure predicts progression toward the metabolic syndrome independently of aerobic fitness in middle-aged healthy Caucasians: the Medical Research Council Ely Study. *Diabetes Care* **28**(5): 1195–200

## DIABETOLOGIA



### Proinsulin better than insulin at predicting CHD

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

**1** Insulin resistance has been linked to atherosclerosis; the extent to which this contributes to the risk of coronary heart disease (CHD) has been examined using plasma immunoreactive insulin concentration.

**2** This marker, however, correlates only moderately with insulin sensitivity as measured with the euglycaemic insulin clamp method (the gold standard); moreover, it is weak as a risk marker for CHD, compared with established markers.

**3** Proinsulin, on the other hand, has been shown to be a long-term predictor of CHD in middle-aged men.

**4** This study aimed to assess the predictive capacity for CHD in older men of various insulin-linked markers.

**5** Data were taken from the Uppsala Longitudinal Study of Adult Men; 815 men aged 70 at baseline were followed up for a maximum of 10 years.

**6** Insulin sensitivity assessed by the euglycaemic insulin clamp was found to be a significant predictor of CHD in this cohort (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.65–0.97).

**7** Intact proinsulin was also found to be a significant predictor (HR, 1.18; 95% CI, 1.10–1.38).

**8** None of specific insulin, plasma immunoreactive insulin and 32–33 split proinsulin had significant predictive capacity.

Zethelius B, Lithell H, Hales CN, Berne C (2005) Insulin sensitivity, proinsulin and insulin as predictors of coronary heart disease. A population-based 10-year, follow-up study in 70-year old men using the euglycaemic insulin clamp. *Diabetologia* **48**(5): 862–7