LETTERS TO THE EDITOR

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Possible involvement of advanced glycation end products in carry-over benefits of atorvastatin in ASCOT-BPLA

I read with interest the recent study by Sever et al.,1 which reported that patients originally assigned atorvastatin continued to demonstrate lower event rates in most cardiovascular endpoints after the termination of Lipid Lowering Arm of the ASCOT (ASCOT-LLA) trial, compared with those originally assigned placebo, although LDL-cholesterol levels were almost identical in the two groups during the 2 years extended follow-up period.2 These observations suggest sustained cardioprotective effects of atorvastatin after the cessation of active treatment in at-risk patients with hypertension. A similar outcome was reported in the DCCT-EDIC Research; it revealed that original intensive therapy for 6.5 years reduced the risk of cardiovascular events to about 50% of that of conventional treatment in diabetic patients 11 years after the end of the trial, although glycosylated haemoglobin values in the two groups had almost converged during the follow-up periods.3 These clinical studies strongly suggest that so-called ‘metabolic memory’ causes chronic vascular damage in high-risk patients with hypertension and diabetes that are not easily reversed, even by subsequent, relatively good control of LDL-cholesterol or blood glucose.

Reducing sugars can react non-enzymatically with amino groups of protein to form Amadori products.3,4 These non-enzymatically with amino groups of LDL-cholesterol or blood glucose. Subsequent, relatively good control of high-risk patients with hypertension and diabetes or oxidative stress conditions, thus playing a role in the development and progression of cardiovascular disease.5,6 Indeed, increased serum or skin levels of AGEs are reported to predict future cardiovascular mortality or progression of diabetic microangiopathy, respectively, in patients with diabetes.6,7 Further, increased formation and accumulation of AGEs are a possible mechanism to explain the ‘metabolic memory’, a long-term beneficial influence of early metabolic control on cardiovascular outcomes. Since we have previously found that atorvastatin not only inhibits the AGE signalling to inflammation in vitro, but also reduces serum levels of AGEs in hypercholesterolemic type 2 diabetic patients,4,7,8 it is conceivable that carry-over beneficial effects of atorvastatin on cardiovascular events in Blood Pressure Lowering Arm of the ASCOT (ASCOT-BPLA) trial could be ascribed, at least in part, to its inhibitory effects on AGE formation and/or the downstream-signalling pathways. Therefore, it is an interesting issue to clarify whether circulating or skin AGE levels at the closure of ASCOT-LLA could predict cardiovascular events at the end of ASCOT-BPLA.

References

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Association of adiponectin with adverse outcome in coronary artery disease patients: results from the AtheroGene study

We read with interest the article by Schnabel et al.1 in which the authors assessed the prognostic value of baseline levels of adiponectin in patients with manifest coronary artery disease (CAD). They conclude that adiponectin concentration is predictive of cardiovascular death or non-fatal myocardial infarction (MI) at a median follow-up of 2.5 years.

Several considerations are worth noting before accepting these conclusions. First, the overall study population is markedly heterogeneous due to the inclusion of patients with stable angina (SA) and various sub-sets of patients with acute coronary syndromes (ACS) (e.g. ST-elevation and non-ST elevation MI). While baseline adiponectin

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levels were almost comparable in both SA and ACS patients, the levels of B-type natriuretic peptide (BNP) and of C-reactive protein (CRP) were more than two-fold higher in patients with ACS than in SA. Both BNP and CRP are known to be associated with adverse outcome in ACS patients, with BNP also having a prognostic role in patients with SA. The BNP levels in the present study were only 38 pg/mL (11.94–99.81) in patients with SA, a range comparable with 36.1 pg/mL (11.3–94.6), a value found in patients with SA who did not have cardiovascular events in a previous study and overlapping with the values of the first and second lower quartiles of BNP, which were not associated with increased risk of cardiovascular events. Second, despite continuous levels of adiponectin predicting cardiovascular events in the overall population after adjusting for the presence of ACS (model 2 regression), adiponectin was not significantly associated with the outcome (models 1–4) in patients with ACS, while only in patients with SA predicted the outcome.

Thirdly, the authors did not report the cardiovascular event rate according to SA and ACS, but it is likely that the patients with SA in this study (who had low BNP values) had a better prognosis compared with patients with ACS.

Taken together, these finding raise the strong possibility that an association between adiponectin and prognosis in patients with ACS might not exist, and that the main result of this study may have been driven by the patients with SA. As patients with ACS represent a large part of patients with CAD in clinical practice, the conclusion, therefore, that adiponectin predicts outcome in patients with CAD may not be accurate.

Moreover, the independent predictive value of adiponectin in SA patients might be a spurious finding, as patients with SA and high levels of BNP (>100 pg/mL) were not included in this study. Furthermore, even in the present cohort of SA patients, a hazard ratio of 1.035 may not represent a clinically significant increase in adverse events if the baseline absolute risk of events is low anyway.

Finally, continuous levels of adiponectin did not independently predict the outcome in the overall population and the independent predictive value of a one-quartile adiponectin level increase has not been verified after entering BNP, CRP, and creatinine as covariates in the Cox proportional hazard regression model.

References

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Association of adiponectin with adverse outcome in coronary artery disease patients: results from the AtheroGene study: reply

We thank Dr Ferrante et al. for their interest in our work. By enrolling consecutive cath lab patients in the AtheroGene cohort, we had the opportunity to evaluate adiponectin concentrations across the entire range of coronary artery disease (CAD) patients. This may be seen as an advantage, but also implies heterogeneity of the cohort which we addressed by presenting our data in the more homogenous subgroups of patients with stable angina (SAP) and acute coronary syndrome (ACS).

In ACS, we observe a similar magnitude and direction of association. Especially in the categorical analysis, it becomes obvious that high concentrations of adiponectin may be related to higher cardiovascular event rates that can be viewed as confirmatory. For survival analysis, we do provide the number of events, which shows, as expected, a higher event rate for ACS patients. These hypothesis generating results need to be prospectively confirmed in ACS cohorts.

We did not exclude participants on the basis of B-type natriuretic peptide (BNP) concentrations. In Model 2 of the statistical regression analysis, adjusting for ACS, adiponectin concentrations remain related to outcome at the 0.05 level. Only after additional adjustment for BNP in the last model, the association becomes borderline when based on the statistical cut-off of 0.05. The effect size and direction remain approximately the same. The two reasons may, in part, account for this: (i) we did not have BNP measurements in all participants, which reduces the power to achieve a statistical threshold, (ii) a positive correlation between adiponectin and BNP is known, which often weakens the effect in a regression analysis.

The value of a biomarker can simplistically be seen as a clinical tool to provide diagnostic or prognostic information to help medical decision making or to provide mechanistic insights. As we point out, the benefit of our data should be seen in the confirmation and extension of recent evidence, that the biomarker adiponectin has a positive biological profile in experimental data, animal models, and human studies in individuals free of symptomatic cardiovascular disease.