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To: Gerstein HC, Pogue J, Mann JFE, Lonn E, Dagenais GR, McQueen M, Yusuf S, for the HOPE investigators (2005) The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia 48:1749–1755

Received: 31 October 2005 / Accepted: 31 October 2005 / Published online: 8 February 2006
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Abbreviations FPG: fasting plasma glucose · UKPDS: UK Prospective Diabetes Study

To the Editor,

In their paper [1], Gerstein and colleagues employ the Heart Outcomes Prevention Evaluation (HOPE) study data in an attempt to pursue their contention that ‘dysglycaemia’ is a risk factor for cardiovascular disease that is independent of recognized categories of glucose intolerance [2]. Their data in diabetic patients, used to assess the relationships of both cardiovascular disease and nephropathy to mean updated glycated haemoglobin levels, are very similar to those from the UK Prospective Diabetes Study (UKPDS) [3], which evaluated a similar number of patients, with glycaemic levels being some 3–4 times more relevant for microvascular than for macrovascular endpoints. I would contend, however, that by attempting to prove a ‘dysglycaemia’ hypothesis (i.e. a continuous relationship between glycaemia and outcome) in non-diabetic subjects, they have ignored one of the conceptual tenets of scientific methodology [4].

The analyses of the ‘progressive relationship’ between baseline fasting plasma glucose (FPG) and relative hazards of four outcomes in 2,950 diabetic and non-diabetic subjects are shown in Fig. 2 of the article adjusted for age and sex, and in Table 3 with a series of additional adjustments [1]. These analyses were performed using Cox regression models with a logarithmic transformation of

FPG as a continuous variable. Yet it is apparent from the figure that the relationships of baseline FPG with cardiovascular events (Fig. 2a), nephropathy (Fig. 2c), and death (Fig. 2d) are anything but linear: for each outcome, the relative hazard of those in the first three quintiles is very similar. So rather than showing a progressive risk, these findings are compatible with a threshold effect. Thus, for cardiovascular risk, the data show a threshold of risk starting in quintile 4 (FPG 6.2–8.5 mmol/l), associated with a relative hazard of around 1.3; the relative hazard is increased to around 1.7 for subjects in quintile 5 (FPG >8.6 mmol/l). For nephropathy, these quintiles show relative hazards of around 2.5 and 8, respectively. These observations might suggest that the threshold for risk is lower for macrovascular than for microvascular disease, something that has been recognised for some 30 years, and led, in 1980, to the introduction of a category of impaired glucose tolerance [5]. However, as quintile 4 includes some subjects with diabetes, as well as subjects with impaired fasting glucose, it is not possible to relate the data in these subjects to categories of glucose intolerance less severe than diabetes.

The use of a Cox regression model treats the data as if the risk is continuous and graded, so that the apparent 10% increase in (age- and sex-adjusted) risk of cardiovascular disease per 1 mmol/l increase in FPG is based on the excess risk in the two highest quintiles. The authors do not report any additional analyses, e.g. use of an additional quadratic term, to assess whether the data were more compatible with a threshold effect. They do mention, however, that self-reported diabetes (of a mean of 10 years’ duration) somewhat reduces the relationship of baseline FPG with cardiovascular disease.

There is overwhelming evidence that diabetes is associated with an approximately two-fold excess risk of cardiovascular disease, and that this excess is not ex-

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plained by conventional risk factors. There is also substantial evidence that lesser degrees of glucose intolerance, particularly as measured after a glucose load [6–8], also predict excess cardiovascular disease. While we have long known that this excess is not explained by blood pressure, dyslipidaemia or obesity, what remains unclear is whether other, unmeasured, risk factors—such as low grade inflammation [9] or endothelial dysfunction [10]—might represent a common antecedent. The concept that the excess risk is the consequence of ‘dysglycaemia’ would require evidence of reversibility (what Bradford Hill referred to as experimentation [11]), and the UKPDS [12] represents an important negative test of the hypothesis.

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