



# Time-varying risk of microvascular complications in latent autoimmune diabetes of adulthood compared with type 2 diabetes in adults: a post-hoc analysis of the UK Prospective Diabetes Study 30-year follow-up data (UKPDS 86)

Ernesto Maddaloni, Ruth L Coleman, Olorunsola Agbaje, Raffaella Buzzetti, Rury R Holman

## Summary

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Experimental Medicine  
Department, Sapienza  
University of Rome, Rome,  
Italy (E Maddaloni MD,  
Prof R Buzzetti MD); and  
Diabetes Trials Unit, Oxford  
Centre for Diabetes,  
Endocrinology and  
Metabolism, University of  
Oxford, Oxford, UK

(E Maddaloni, R L Coleman MSc,  
O Agbaje MSc,  
Prof R R Holman FRCP)

Correspondence to:  
Dr Ernesto Maddaloni,  
Experimental Medicine  
Department, Sapienza University  
of Rome, Rome 00139, Italy  
[ernesto.maddaloni@uniroma1.it](mailto:ernesto.maddaloni@uniroma1.it)

**Background** Latent autoimmune diabetes of adulthood (LADA) differs in clinical features from type 2 diabetes. Whether this difference translates into different risks of complications remains controversial. We examined the long-term risk of microvascular complications in people enrolled in the UK Prospective Diabetes Study (UKPDS), according to their diabetes autoimmunity status.

**Methods** We did a post-hoc analysis of 30-year follow-up data from UKPDS (UKPDS 86). UKPDS participants with diabetes autoantibody measurements available and without previous microvascular events were included. Participants with at least one detectable autoantibody were identified as having latent autoimmune diabetes, and those who tested negative for all autoantibodies were identified as having type 2 diabetes. The incidence of the primary composite microvascular outcome (first occurrence of renal failure, renal death, blindness, vitreous haemorrhage, or retinal photocoagulation) was compared between adults with latent autoimmune diabetes and those with type 2 diabetes. The follow-up ended on Sept 30, 2007. Baseline and updated 9-year mean values of potential confounders were tested in Cox models to adjust hazard ratios (HRs). UKPDS is registered at the ISRCTN registry, 75451837.

**Findings** Among the 5028 participants included, 564 had latent autoimmune diabetes and 4464 had type 2 diabetes. After median 17·3 years (IQR 12·6–20·7) of follow-up, the composite microvascular outcome occurred in 1041 (21%) participants. The incidence for the composite microvascular outcome was 15·8 (95% CI 13·4–18·7) per 1000 person-years in latent autoimmune diabetes and 14·2 (13·3–15·2) per 1000 person-years in type 2 diabetes. Adults with latent autoimmune diabetes had a lower risk of the composite outcome during the first 9 years of follow-up than those with type 2 diabetes (adjusted HR 0·45 [95% CI 0·30–0·68],  $p < 0·0001$ ), whereas in subsequent years their risk was higher than for those with type 2 diabetes (1·25 [1·01–1·54],  $p = 0·047$ ). Correcting for the higher updated 9-year mean HbA<sub>1c</sub> seen in adults with latent autoimmune diabetes than in those with type 2 diabetes explained entirely their subsequent increased risk for the composite microvascular outcome (adjusted HR 0·99 [95% CI 0·80–1·23],  $p = 0·93$ ).

**Interpretation** At diabetes onset, adults with latent autoimmune diabetes have a lower risk of microvascular complications followed by a later higher risk of complications than do adults with type 2 diabetes, secondary to worse glycaemic control. Implementing strict glycaemic control from the time of diagnosis could reduce the later risk of microvascular complications in adults with latent autoimmune diabetes.

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## Introduction

Diabetes-related autoantibodies are detectable in 2–12% of adults with a clinical diagnosis of type 2 diabetes.<sup>1–3</sup> These people are affected by a mild form of autoimmune diabetes known as latent autoimmune diabetes of adulthood (LADA). An overlap in the pathogenesis and clinical features of type 2 diabetes and type 1 diabetes has been hypothesised in latent autoimmune diabetes.<sup>4</sup>

Diabetic microvascular complications are a major cause of end-stage renal disease and blindness worldwide.<sup>5,6</sup> We have previously shown a similar risk of major cardiovascular events in latent autoimmune

diabetes and type 2 diabetes.<sup>7</sup> However, the prevalence of microvascular complications might differ among diabetes types because of different pathogenesis and prevalence of risk factors, but data in this regard are scarce. The comparative evaluation of vascular complications between different forms of diabetes could aid in risk stratification, which is essential to help promote individualised prevention of complications and treatment strategies. Furthermore, it might show crucial differences in risk factors, which could have an impact on the understanding of the pathogenesis of complications in the different forms of diabetes. In this regard,

## Research in context

### Evidence before this study

In a systematic review published in 2017, we reviewed original articles reporting the risk of complications in latent autoimmune diabetes of adulthood. Taken together, these studies suggested a lower prevalence of microvascular complications in latent autoimmune diabetes compared with type 2 diabetes in patients with short disease duration and an opposite picture in patients with longer disease duration, with uncertainties about the factors explaining this time-dependent difference. To update the evidence, we searched PubMed for articles published up to Oct 1, 2019, with the following search criteria: "latent autoimmune diabetes of the adults" or "LADA" AND "retinopathy" or "nephropathy" or "complications". Most studies that had investigated this topic were, however, limited by small sample sizes and by heterogeneity among the individuals enrolled with respect to ethnicity, metabolic control, and disease duration. We have shown previously that the risk of cardiovascular disease does not differ between latent autoimmune diabetes and type 2 diabetes after adjusting for risk factors. Whether this is true also for microvascular complications needs to be clarified.

### Added value of this study

The UK Prospective Diabetes Study has the largest population of adults with latent autoimmune diabetes, with the longest follow-up ever evaluated in a randomised clinical trial for diabetes complications. The enrolment of patients with newly

diagnosed type 2 diabetes, the adjudication of hard clinical outcomes, the full availability of risk factor data measured at several timepoints, and a follow-up of up to 30 years permit a more detailed comparison of the natural history of microvascular complications in adults with latent autoimmune diabetes and those with type 2 diabetes. Our study provides insights into the association between diabetes heterogeneity and microvascular complications, showing that patients with latent autoimmune diabetes have a lower risk of developing microvascular complications over 9 years from diagnosis than do those with type 2 diabetes, and that their subsequent higher risk can be explained by their earlier worse glycaemic control.

### Implications of all the available evidence

Complication risk stratification is essential to help promote individualised prevention of complications in type 2 diabetes and to inform treatment strategies. In this regard, the comparative evaluation of vascular complication risks between the different forms of diabetes is an open research area. Results of this study might allow tailored screening strategies and highlight the existence of an early therapeutic window in latent autoimmune diabetes to improve microvascular outcomes by implementing strict glycaemic control. Randomised controlled trials are needed to test the efficacy of antidiabetes therapy for improving glycaemic control and microvascular outcomes in latent autoimmune diabetes.

data from the Diabetes Control and Complications Trial<sup>8</sup> suggested that preserved  $\beta$ -cell secretion of insulin is associated with lower incidence of retinopathy and nephropathy in type 1 diabetes. Differences in auto-antibody concentrations also affect clinical features of patients with latent autoimmune diabetes.<sup>9</sup> However, whether  $\beta$ -cell function and autoimmune load are linked to microvascular complications in latent autoimmune diabetes has not been determined.

In this study, we aimed to evaluate the long-term risk of microvascular complications and the factors affecting this risk in latent autoimmune diabetes compared with type 2 diabetes in the large population of adults with a clinical diagnosis of new-onset type 2 diabetes enrolled in the UK Prospective Diabetes Study (UKPDS). Furthermore, we explored whether allocation to intensive, compared with conventional, glycaemic control strategies had different effects on microvascular complications in adults with latent autoimmune diabetes or type 2 diabetes.

## Methods

### Study design and population

We did a post-hoc analysis of 30-year follow-up data from UKPDS (UKPDS 86). The UKPDS protocol, design, and methods have been reported previously.<sup>10</sup> 5102 participants aged 25–65 years with type 2 diabetes newly diagnosed by

their general practitioner, and with a fasting plasma glucose (FPG) concentration of more than 6 mmol/L on two subsequent occasions, were enrolled in UKDPS between 1977 and 1991.<sup>11</sup> A further 2514 patients were excluded according to the following criteria: severe vascular disease (myocardial infarction in the past year, current angina, or heart failure); accelerated hypertension; proliferative or pre-proliferative retinopathy; renal failure with plasma creatinine of more than 175  $\mu$ mol/L; other life-threatening disease such as cancer; an illness requiring systemic steroids; an occupation precluding insulin treatment; unfamiliarity with English; and ketonuria greater than 3 mmol/L suggestive of type 1 diabetes.<sup>10</sup> Briefly, after a 3-month dietary run-in period, patients with a FPG concentration of more than 6 mmol/L and less than 15 mmol/L were randomly assigned to a conventional glucose control strategy (primarily diet) or to an intensive glucose control strategy (sulfonylurea or insulin, or [if >120% of ideal bodyweight] metformin), and followed quarterly in UKPDS clinics. HbA<sub>1c</sub>, total cholesterol, HDL cholesterol, LDL cholesterol, FPG, and insulin were measured yearly. Estimated glomerular filtration rate (eGFR) was calculated every 3 years.<sup>12</sup> Following close-out of the interventional trial on Sept 30, 1997, all surviving patients entered a 10-year post-trial observational monitoring programme, as reported

previously.<sup>13</sup> During this period, no attempt was made to continue treatment with previously randomised therapies. Participants were seen annually for 5 years in UKPDS clinics, with continued standardised collection of outcome data, measurements of blood pressure, FPG, HbA<sub>1c</sub>, plasma creatinine, and the ratio of urinary albumin to creatinine. Homoeostasis model assessment 2 (HOMA2)<sup>14</sup> was used to estimate steady-state  $\beta$ -cell function (HOMA2-B) and insulin resistance (HOMA2-IR) using the HOMA calculator. For the second 5 years, participants were followed remotely via questionnaires. This study followed the Helsinki guidelines, and the study protocol was approved by the ethics committee of all 23 UKPDS clinical centres. All patients gave written informed consent to participate.

### Procedures

One or more of the autoantibodies against islet cell autoantigen (ICA), glutamic acid decarboxylase (GADA), and protein tyrosine phosphatase isoforms IA-2 (IA-2A) were measured as previously described<sup>2,15,16</sup> in 5096 (99.9%) UKPDS participants. Only 1.2% of autoantibody samples were taken more than 2 years after diagnosis.<sup>15</sup> Participants were identified as having latent autoimmune diabetes if

they tested positive for at least one autoantibody (ICA, GADA, or IA-2A). Participants were confirmed as having type 2 diabetes if they tested negative for all measured autoantibodies. Since one negative autoantibody test does not exclude latent autoimmune diabetes, we did not include in this analysis the 34 participants with one negative autoantibody measurement and no data for either of the other two autoantibodies. Among the 5062 remaining participants, a further 34 were excluded from this analysis because they had a previous microvascular event, leaving 5028 participants included in this study.

Participants who tested positive for both GADA and IA-2A were defined as double autoantibody positive for subgroup analyses. Since both GAD and IA-2A are islet cell antigens, an overlap of ICA with both GADA and IA-2A might exist. Therefore, the simultaneous presence of GADA and ICA or of IA-2A and ICA was not considered a sufficient condition to define double positivity.

To test whether the degree of baseline  $\beta$ -cell function and the concentration of autoantibodies affected the risk of the microvascular outcome in latent autoimmune diabetes, participants with latent autoimmune diabetes were further stratified into two categories according to their median HOMA2-B (40.7% [IQR 19.6–62.3]) as low HOMA2-B (HOMA2-B  $\leq$ 40.7%) or high HOMA2-B (HOMA2-B >40.7%) and into other two categories according to median values of GADA (84 U/L [38–103]), IA-2A (33.2 U [6.1–77.6]), and ICA (45 U [15–80]) as high autoantibody concentration (at least one autoantibody with concentration above the median) and low autoantibody concentration (no autoantibody with concentration above the median). Median values of autoantibodies were calculated among patients positive for that specific autoantibody.

### Outcomes

The primary outcome was the same composite hard microvascular outcome as in UKPDS: first occurrence of renal failure (defined by dialysis or plasma creatinine >250  $\mu$ mol/L not related to any intercurrent illness), death from renal disease, blindness in one eye (defined by Snellen-chart visual acuity of 6/60 or worse, or Early Treatment of Diabetic Retinopathy Study logarithm of the minimum angle of resolution [logMAR] 1.0 or worse, for 3 months), vitreous haemorrhage, or retinal photocoagulation.<sup>11</sup> The secondary outcomes were nephropathy (defined as renal failure or death from renal disease) and retinopathy (defined as blindness in one eye, vitreous haemorrhage, or retinal photocoagulation) separately, as more recent evidence suggests that these outcomes might not cluster together.<sup>17,18</sup>

### Statistical analysis

We present descriptive statistics for categorical variables as numbers with proportions, and for continuous variables as appropriate measures of central tendency and dispersion.

For the HOMA calculator see  
www.dtu.ox.ac.uk/  
homacalculator/

|                                                                     | Latent autoimmune diabetes (n=564) | Type 2 diabetes (n=4464) | p value |
|---------------------------------------------------------------------|------------------------------------|--------------------------|---------|
| Age, years                                                          | 50.4 (40.4–58.1)                   | 54.0 (47.4–59.5)         | <0.0001 |
| Sex                                                                 | ..                                 | ..                       | 0.11    |
| Male                                                                | 314 (56%)                          | 2641 (59%)               | ..      |
| Female                                                              | 250 (44%)                          | 1823 (41%)               | ..      |
| Race                                                                | ..                                 | ..                       | <0.0001 |
| White                                                               | 528 (94%)                          | 3614 (81%)               | ..      |
| Black                                                               | 11 (2%)                            | 363 (8%)                 | ..      |
| Other*                                                              | 25 (4%)                            | 487 (11%)                | ..      |
| Smoking status†                                                     | ..                                 | ..                       | 0.070   |
| Current                                                             | 197 (35%)                          | 1361/4462 (30%)          | ..      |
| Former                                                              | 170 (30%)                          | 1512/4462 (34%)          | ..      |
| Never                                                               | 197 (35%)                          | 1589/4462 (36%)          | ..      |
| BMI, kg/m <sup>2</sup>                                              | 24.2 (21.8–27.6)                   | 26.8 (24.1–30.4)         | <0.0001 |
| Systolic blood pressure, mm Hg                                      | 128 (116–140)                      | 135 (122–148)            | <0.0001 |
| HbA <sub>1c</sub> , %                                               | 7.3% (6.2–9.2)                     | 6.8% (5.9–8.0)           | <0.0001 |
| HbA <sub>1c</sub> , mmol/mol                                        | 56 (44–77)                         | 51 (41–64)               | ..      |
| Total cholesterol, mmol/L                                           | 5.2 (4.4–5.9)                      | 5.3 (4.6–6.0)            | 0.0078  |
| LDL cholesterol, mmol/L                                             | 3.3 (2.7–4.1)                      | 3.4 (2.8–4.1)            | 0.12    |
| HDL cholesterol, mmol/L                                             | 1.07 (0.92–1.23)                   | 1.04 (0.91–1.20)         | 0.011   |
| Triglycerides, mmol/L                                               | 1.3 (0.9–1.8)                      | 1.5 (1.1–2.1)            | <0.0001 |
| Estimated glomerular filtration rate, mL/min per 1.73m <sup>2</sup> | 81.6 (65.0–103.3)                  | 77.6 (62.1–100.2)        | 0.0014  |
| HOMA2-B, %                                                          | 40.7% (19.6–62.3)                  | 49.9% (30.7–73.7)        | <0.0001 |
| HOMA2-IR, %                                                         | 1.3% (0.9–1.9)                     | 1.6% (1.1–2.3)           | <0.0001 |

Data are median (IQR) or n (%). Proportions might not sum to 100% as a result of round-up. HOMA2-B=homoeostasis model assessment 2 for  $\beta$ -cell function. HOMA2-IR=homoeostasis model assessment 2 for insulin resistance.  
\*Asian Indian, Asian Chinese, and other races. †Two patients with type 2 diabetes had no data about smoking status.

Table 1: Baseline characteristics by diabetes autoimmunity status

We tested the distributions of variables for normality with the Shapiro-Wilk test. We compared continuous variables with a parametric distribution between groups using the Student's *t* test, and we used the Kruskal-Wallis test for non-parametric variables. We compared categorical variables with a  $\chi^2$  or Fisher's exact test as appropriate. We used multivariable analysis of variance to evaluate the effect of latent autoimmune diabetes status on multiple variables, with non-parametric variables logarithmically transformed (natural log) before entering the model.

We did time-to-first-event analyses comparing participants with latent autoimmune diabetes and those with type 2 diabetes for the primary and secondary microvascular outcomes using Cox regression models and Kaplan-Meier plots. Data were censored on Sept 30, 2007. We also used Cox regression models and Kaplan-Meier plots for latent autoimmune diabetes subgroup analyses. We tested the proportional-hazards assumption using Schoenfeld residuals and graphically. If this assumption was violated, we used time-varying Cox models with interaction between diabetes groups and time. In subgroup analyses, we tested regression coefficients of subgroups for equality. Potential baseline confounders were tested within all Cox models and retained if their effect remained nominally significant ( $p < 0.1$ ): age, HbA<sub>1c</sub>, BMI, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, eGFR, and systolic blood pressure (SBP) were included as continuous variables; and smoking status, randomisation group, and race were included as categorical variables. We calculated updated 9-year mean values of BMI, SBP, HbA<sub>1c</sub>, total cholesterol, HDL cholesterol, and LDL cholesterol as the average of all available yearly measurements from year 1 to year 9 for patients with at least one available measurement between the first and the ninth year after enrolment and tested them in Cox models 2 and 3. Missing risk factor data were imputed using multiple imputation (complete list of missing values available in the appendix p 1).<sup>19</sup>

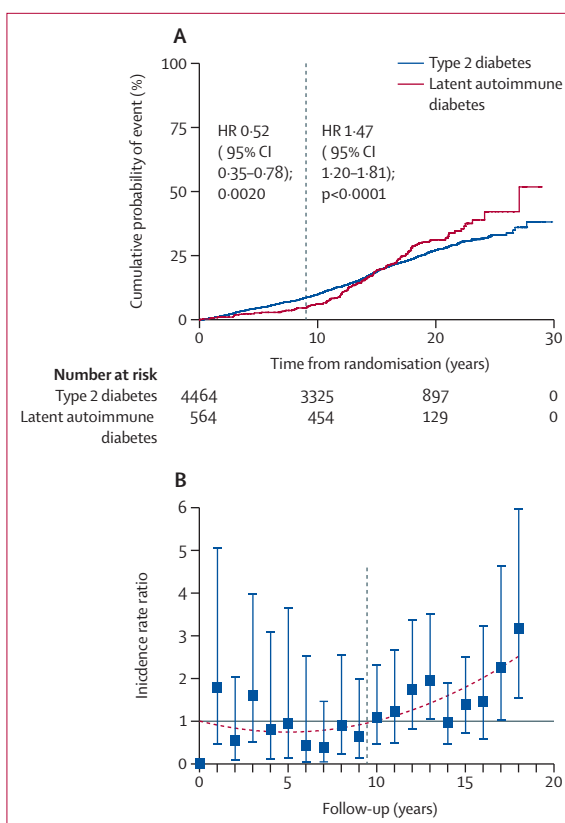
Cox regression was used to evaluate the effect of the randomised glycaemic control strategy on the composite microvascular outcome. To investigate whether this effect differed between latent autoimmune diabetes and type 2 diabetes, subgroup analyses were done by fitting interaction terms between randomisation groups and diabetes types. We also analysed outcomes by auto-antibody subgroups.

Two-sided tests at the 0.05 level of significance were used for all statistical comparisons, with Stata/IC 12.1 software and Prism 8.0d Software used for data analysis and graphical representations.

UKPDS is registered at the ISRCTN registry, number 75451837.

### Role of the funding source

The funder was not involved in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the



**Figure 1: Time-varying risk of microvascular events in latent autoimmune diabetes**

Kaplan-Meier failure curves and unadjusted HRs for the composite microvascular outcome in adults with latent autoimmune diabetes versus those with type 2 diabetes (A), and yearly incident ratios between participants with latent autoimmune diabetes and those with type 2 diabetes with fitted quadratic polynomial non-linear regression line (dashed red line; B). Error bars indicate 95% CI. Dashed vertical grey lines in both panels represent the 9-year change in the hazards cut point. HR=hazard ratio.

paper for publication. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

See Online for appendix

### Results

564 (11%) of 5028 UKPDS participants included in these analyses were categorised as having latent autoimmune diabetes, and 4464 (89%) were identified as having type 2 diabetes. At diabetes onset, participants with latent autoimmune diabetes were younger ( $p < 0.0001$ ), more frequently white ( $p < 0.0001$ ), with a lower BMI ( $p < 0.0001$ ), higher HDL cholesterol ( $p = 0.011$ ), lower total cholesterol ( $p = 0.0078$ ), lower triglycerides ( $p < 0.0001$ ), lower SBP ( $p < 0.0001$ ), lower HOMA-B ( $p < 0.0001$ ), lower HOMA-IR ( $p < 0.0001$ ), and higher HbA<sub>1c</sub> ( $p < 0.0001$ ) than those with type 2 diabetes (table 1).

After a median 17.3 years (IQR 12.6–20.7) of follow-up, the composite microvascular outcome occurred in 1041 (21%) participants, comprising 65 renal and 976 retinopathy events. The incidence for the composite

|                                                | Incidence per 1000 person-years (95% CI) |                          | HR (95% CI)      | p value | Model 1* adjusted HR (95% CI) | p value | Model 2† adjusted HR (95% CI) | p value | Model 3‡ adjusted HR (95% CI) | p value |
|------------------------------------------------|------------------------------------------|--------------------------|------------------|---------|-------------------------------|---------|-------------------------------|---------|-------------------------------|---------|
|                                                | Latent autoimmune diabetes (n=564)       | Type 2 diabetes (n=4464) |                  |         |                               |         |                               |         |                               |         |
| <b>Primary composite microvascular outcome</b> |                                          |                          |                  |         |                               |         |                               |         |                               |         |
| First 9 years (387 first events)               | 5.3 (3.5–7.8)                            | 10.0 (9.1–11.1)          | 0.52 (0.35–0.78) | 0.0020  | 0.45 (0.30–0.68)              | <0.0001 | NA                            | NA      | NA                            | NA      |
| Beyond 9 years (654 first events)              | 13.6 (11.3–16.4)                         | 9.2 (8.5–10.0)           | 1.47 (1.20–1.81) | <0.0001 | 1.25 (1.01–1.54)              | 0.047   | 1.33 (1.07–1.64)              | 0.012   | 0.99 (0.80–1.23)              | 0.93    |
| <b>Retinopathy</b>                             |                                          |                          |                  |         |                               |         |                               |         |                               |         |
| First 9 years (372 first events)               | 5.3 (3.5–7.8)                            | 9.6 (8.7–10.7)           | 0.55 (0.36–0.82) | 0.0030  | 0.46 (0.31–0.69)              | <0.0001 | NA                            | NA      | NA                            | NA      |
| Beyond 9 years (611 first events)              | 12.5 (10.3–15.1)                         | 8.6 (7.9–9.4)            | 1.44 (1.16–1.78) | 0.0010  | 1.19 (0.95–1.48)              | 0.12    | 1.29 (1.04–1.62)              | 0.024   | 0.98 (0.79–1.22)              | 0.86    |
| <b>Nephropathy</b>                             |                                          |                          |                  |         |                               |         |                               |         |                               |         |
| First 9 years (27 first events)                | 0                                        | 0.7 (0.5–1.1)            | 0                | NA      | NA                            | NA      | NA                            | NA      | NA                            | NA      |
| Beyond 9 years (81 first events)               | 1.3 (0.8–2.3)                            | 1.0 (0.8–1.3)            | 1.26 (0.68–2.32) | 0.46    | NA                            | NA      | NA                            | NA      | NA                            | NA      |

HR=hazard ratio. NA=not applicable. \*Baseline covariates retained at a p<0.1 were HbA<sub>1c</sub>, systolic blood pressure, smoking status, and randomisation group. †Covariates retained at a p<0.1 were baseline HbA<sub>1c</sub>, smoking status, and randomisation group, plus updated 9-year mean BMI and systolic blood pressure (baseline systolic blood pressure not significant at p<0.1). ‡Covariates retained at a p<0.1 were same as model 2 plus updated 9-year mean HbA<sub>1c</sub>.

**Table 2: Incidence and hazard ratios for microvascular outcomes**

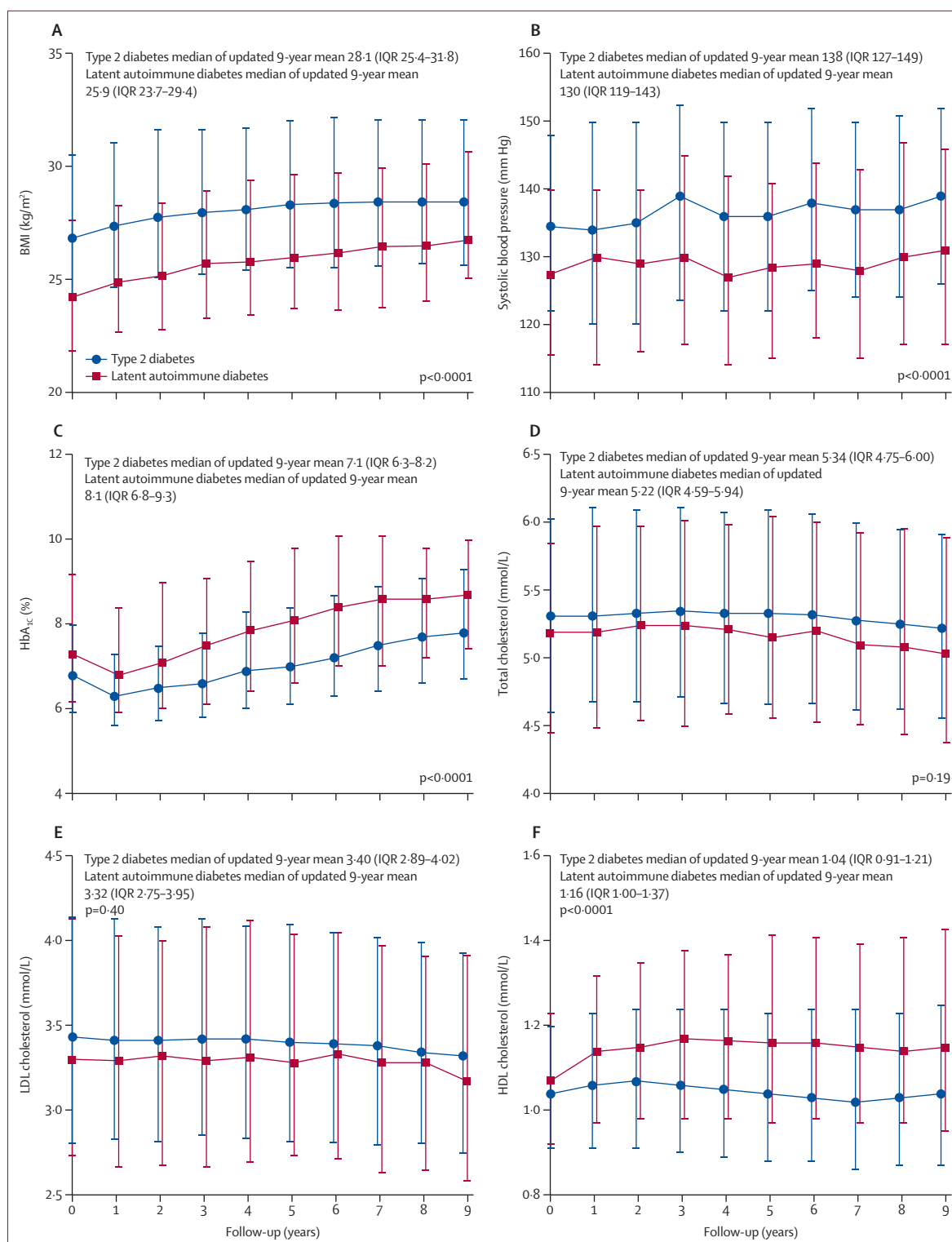
microvascular outcome was 15.8 (95% CI 13.4–18.7) per 1000 person-years in latent autoimmune diabetes and 14.2 (13.3–15.2) per 1000 person-years in type 2 diabetes. The Kaplan-Meier failure curve showed non-proportional hazards with the effect of latent autoimmune diabetes on the composite microvascular outcome changing over time compared with type 2 diabetes (figure 1A). This finding was confirmed by a time-varying Cox-regression analysis that showed a significant interaction between latent autoimmune diabetes and type 2 diabetes status with time (p<0.0001). Hazard plots over time showed that for patients with type 2 diabetes, the hazards were constant over the entire follow-up, and those for patients with latent autoimmune diabetes varied over time (appendix p 2). Fitting a quadratic polynomial non-linear regression to the yearly incidence rate ratio between latent autoimmune diabetes and type 2 diabetes showed that the mean incidence rate ratio transitioned between less than 1 and more than 1 at 9 years (figure 1B). A Cox regression model, stratified for time, showed that during the first 9 years from the diagnosis, patients with latent autoimmune diabetes had a lower risk of the composite microvascular outcome than patients with type 2 diabetes (HR 0.52 [95% CI 0.35–0.78], p=0.0020), whereas for subsequent years it was higher than for patients with type 2 diabetes (1.47 [1.20–1.81], p<0.0001; figure 1A). Correcting for other baseline risk factors associated with the composite microvascular outcome (HbA<sub>1c</sub>, SBP, smoking status, and randomisation group) decreased these HRs to 0.45

(95% CI 0.30–0.68, p<0.0001) for the first 9 years and 1.25 (1.01–1.54, p=0.047) beyond 9 years (table 2).

The incidences and HRs for retinal events were similar to those observed for the composite microvascular outcome both in the unadjusted and in the adjusted analyses (table 2). No patients with latent autoimmune diabetes had any renal event during the first 9 years of follow-up, compared with the incidence of 0.7 (95% CI 0.5–1.1) per 1000 person-years observed in type 2 diabetes. In subsequent years, the incidence of renal events increased in patients with latent autoimmune diabetes to 1.3 (95% CI 0.8–2.3) per 1000 person-years and remained constant in type 2 diabetes (1.0 [0.8–1.3] per 1000 person-years; table 2). The low number of renal events did not allow for adjusted analyses for this specific outcome.

Over the first 9 years of follow-up, patients with latent autoimmune diabetes had higher mean HbA<sub>1c</sub> (p<0.0001) and HDL cholesterol (p<0.0001), and lower mean BMI (p<0.0001) and SBP (p<0.0001). Total cholesterol and LDL cholesterol did not differ significantly between latent autoimmune diabetes and type 2 diabetes during this time period (figure 2).

Updated 9-year mean HbA<sub>1c</sub>, SBP, and BMI were significantly associated with the composite microvascular outcome (p<0.0001 for HbA<sub>1c</sub> and SBP; p=0.045 for BMI) and were therefore tested in the Cox model according to autoimmunity status. Adjusting for updated 9-year mean SBP and BMI did not change the HR significantly for the composite microvascular outcome in latent autoimmune diabetes versus type 2 diabetes beyond 9 years from



**Figure 2: Clinical and biochemical features during the first 9 years of follow-up**

Clinical and biochemical variables during the first 9 years of follow-up in participants with latent autoimmune diabetes and those with type 2 diabetes, showing annual median (IQR) for BMI (A), systolic blood pressure (B), HbA<sub>1c</sub> (C), total cholesterol (D), LDL cholesterol (E), and HDL cholesterol (F). Median (IQR) values of the updated 9-year mean values for each variable are also reported. Error bars indicate IQRs.

|                                                              | First 9 years of follow-up | p value (adjusted p value) for difference between subgroups | Follow-up beyond 9 years | p value for difference between subgroups |
|--------------------------------------------------------------|----------------------------|-------------------------------------------------------------|--------------------------|------------------------------------------|
| All adults with latent autoimmune diabetes (n=564)           | 0.52 (0.35-0.78)           | ..                                                          | 1.47 (1.20-1.81)         | ..                                       |
| Single autoantibody positive vs double autoantibody positive | ..                         | 0.0030 (adjusted 0.0020)                                    | ..                       | 0.76                                     |
| Single autoantibody positive (n=482)                         | 0.61 (0.42-0.88)           | ..                                                          | 1.47 (1.18-1.82)         | ..                                       |
| Double autoantibody positive (n=82)                          | 0.23 (0.10-0.55)           | ..                                                          | 1.36 (0.87-2.14)         | ..                                       |
| Low autoantibody titre vs high autoantibody titre            | ..                         | 0.0030 (adjusted 0.0010)                                    | ..                       | 0.99                                     |
| Low autoantibody titre (n=289)                               | 0.75 (0.53-1.04)           | ..                                                          | 1.46 (1.11-1.91)         | ..                                       |
| High autoantibody titre (n=275)                              | 0.38 (0.21-0.67)           | ..                                                          | 1.46 (1.12-1.88)         | ..                                       |
| Low HOMA2-B vs high HOMA2-B                                  | ..                         | 0.010 (adjusted 0.88)                                       | ..                       | 0.53                                     |
| Low HOMA2-B (n=216)                                          | 0.92 (0.64-1.32)           | ..                                                          | 1.55 (1.16-2.07)         | ..                                       |
| High HOMA2-B (n=215)                                         | 0.48 (0.26-0.89)           | ..                                                          | 1.37 (1.00-1.89)         | ..                                       |

Data are hazard ratio (95% CI) unless otherwise stated. p values are shown before and after adjustment for baseline confounders. HOMA2-B=homoeostasis model assessment 2 for  $\beta$ -cell function.

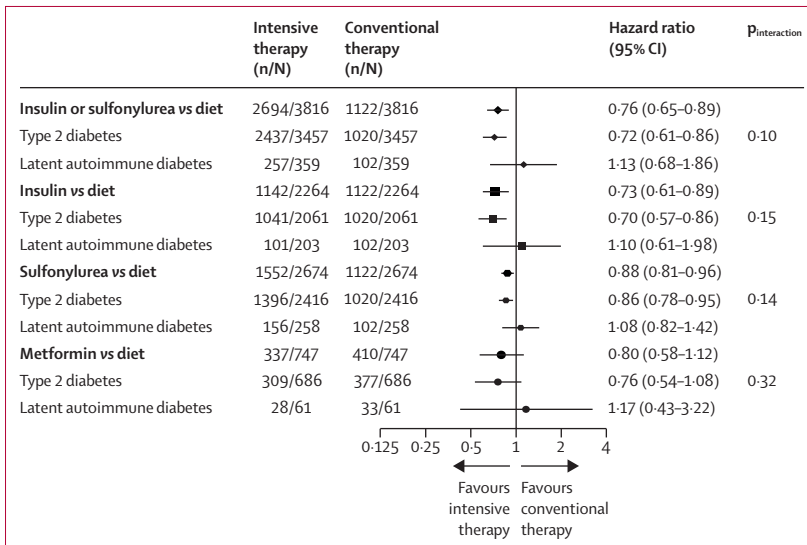
**Table 3: Hazard ratios for the primary composite microvascular outcome by latent autoimmune diabetes subgroups**

After correcting for the updated 9-year mean HbA<sub>1c</sub>, the association between BMI and the composite microvascular outcome disappeared.

Among participants with latent autoimmune diabetes, 482 (85%) had only one detectable autoantibody and 82 (14%) were double autoantibody positive. At diabetes onset, participants with double autoantibody positivity were younger ( $p < 0.0001$ ), more frequently white ( $p = 0.032$ ), with a lower BMI ( $p = 0.0016$ ), lower SBP ( $p < 0.0001$ ), lower HOMA2-B ( $p < 0.0001$ ), lower HOMA-IR ( $p = 0.047$ ) and higher HbA<sub>1c</sub> ( $p = 0.012$ ) than participants with latent autoimmune diabetes and only one autoantibody (appendix p 1). Similar differences in baseline features were also found in subgroups of autoantibody titre and of HOMA2-B levels (data not shown).

During the first 9-years of follow-up, the HR for the composite microvascular outcome was 0.61 (95% CI 0.42-0.88) in single autoantibody-positive participants and 0.23 (0.10-0.55) in double autoantibody-positive participants ( $p = 0.0030$ ; table 3). Similarly, the first 9-year HR was 0.75 (95% CI 0.53-1.04) in participants with low autoantibody concentration and 0.38 (0.21-0.67) in participants with high autoantibody concentration ( $p = 0.0030$ ), 0.92 (0.64-1.32) in the low HOMA2-B group, and 0.48 (0.26-0.89) in the high HOMA2-B group ( $p = 0.010$ ). The heterogeneity observed in latent autoimmune diabetes subgroups of autoantibody number and titre, but not in subgroups of baseline HOMA2-B, was independent from baseline confounders (table 3). No significant effect of any latent autoimmune diabetes subgroup on the outcome was observed during the subsequent follow-up beyond 9 years (table 3; appendix pp 3-4).

During the interventional trial, participants randomly assigned to the intensive glycaemic control strategy therapy had a lower risk of the composite microvascular endpoint than did those assigned to the conventional therapy (HR 0.76 [95% CI 0.65-0.89],  $p = 0.0008$ ; data not shown). This lower risk was still evident at the end of the post-trial monitoring period (HR 0.78 [95% CI 0.67-0.91],  $p = 0.0015$ ; data not shown). Participants randomly assigned to metformin had a similar risk of microvascular events to participants assigned to diet alone both at the end of the trial (HR 0.80 [95% CI 0.58-1.12],  $p = 0.19$ ) and at the end of the post-trial monitoring period (0.81 [0.59-1.10],  $p = 0.18$ ; data not shown). Subgroup analyses by latent autoimmune diabetes status did not show any significant difference in the effect of the assigned glycaemic strategy between latent autoimmune diabetes and type 2 diabetes (all p values for interaction  $> 0.05$ ; figure 3).



**Figure 3: Subgroup analysis of the UK Prospective Diabetes Study by latent autoimmune diabetes status** Effect of assigned intensive glycaemic therapies compared with conventional treatment (primarily diet), on the composite microvascular endpoint, overall and by latent autoimmune diabetes and type 2 diabetes status.

diagnosis (model 2 in table 2). However, correcting for the updated 9-year mean HbA<sub>1c</sub> entirely explained the greater risk beyond 9 years observed for the composite microvascular outcome in patients with latent autoimmune diabetes than in those with type 2 diabetes (adjusted HR 0.99 [95% CI 0.80-1.23],  $p = 0.93$ ; model 3 in table 2).

### Discussion

This post-hoc analysis of UKPDS 30-year follow-up data shows a monotonic increase over time for the risk of the composite microvascular outcome in people with type 2 diabetes, whereas the risk in people with latent

autoimmune diabetes varies. During the first 9 years from diagnosis of diabetes, patients with latent autoimmune diabetes, who were younger and leaner with a lower median SBP and insulin resistance than those with type 2 diabetes, had a 55% lower adjusted risk for the composite microvascular outcome. Beyond 9 years, however, the situation was reversed, with patients with latent autoimmune diabetes having a 33% greater adjusted risk for the composite microvascular outcome than those with type 2 diabetes. This increased risk in latent autoimmune diabetes beyond 9 years was explained entirely by their higher updated mean 9-year HbA<sub>1c</sub> values, which probably reflects their 0·5% absolute higher baseline HbA<sub>1c</sub> values and approximately 10% absolute lower median baseline HOMA2-B, which could have affected the effectiveness of their glucose-lowering therapies.

The lower risk of microvascular complications during the first 9 years of follow-up and the increased risk beyond 9 years were confirmed in all latent autoimmune diabetes subgroups, with an even lower risk during the first 9 years in participants with latent autoimmune diabetes who were positive for more than one autoantibody or with high autoantibody titre.

In addition, the lower risk for the composite microvascular outcome with an intensive, compared with a conventional, glycaemic control strategy did not differ between participants with latent autoimmune diabetes and those with type 2 diabetes.

The time-varying risk for the composite microvascular outcome we observed in this study for participants with latent autoimmune diabetes agrees with an overall evaluation of previous studies comparing retinopathy and nephropathy risks between patients with latent autoimmune diabetes and those with type 2 diabetes. Taken together, results from cross-sectional studies<sup>20–25</sup> suggest that microvascular complications are more rarely observed in patients with latent autoimmune diabetes than in those with type 2 diabetes close to the time when diabetes is diagnosed, whereas an opposite pattern is observed later in the disease history.<sup>4</sup> Data from the longitudinal observational Fremantle Diabetes Study (FDS) showed similar incidence of retinopathy and lower incidence of microalbuminuria in 45 patients with latent autoimmune diabetes to more than 1000 patients with type 2 diabetes over a mean follow-up of 3·7–4·4 years.<sup>26</sup> An analysis of the Collaborative Atorvastatin Diabetes Study (CARDS) showed no difference in incident albuminuria and proliferative retinopathy between patients with latent autoimmune diabetes and those with type 2 diabetes over 4 years of follow-up.<sup>27</sup> All of these studies were, however, limited by small sample sizes, the scarcity of data about risk factor control over time, the cross-sectional study design, or relatively short follow-up periods. Furthermore, in both FDS and CARDS, there was a large heterogeneity of disease duration, which could have masked the prevalent effect of diabetes exposure time on the incidence of microvascular events.

The UKPDS long-term dataset facilitated a more robust evaluation of baseline and time-varying changes in classic risk factors associated with microvascular complications. In the final multivariable model, smoking status, SBP, and HbA<sub>1c</sub> were the only modifiable risk factors to be retained, suggesting that they should be considered as therapeutic targets to prevent microvascular disease in patients with latent autoimmune diabetes. In particular, the fact that the post 9-year 33% higher risk for the composite microvascular outcome in participants with latent autoimmune diabetes is explained entirely by their higher updated 9-year mean HbA<sub>1c</sub> values suggests that immediate and maintained implementation of strict glycaemic control is crucial for patients with latent autoimmune diabetes to minimise their risk of microvascular complications, with previous UKPDS reports showing that 1% reduction in HbA<sub>1c</sub> is associated with a 37% (95% CI 33–41) reduced risk of microvascular disease.<sup>28</sup>

The lower risk of microvascular complications during the first years after the diagnosis of latent autoimmune diabetes needs further examination. One hypothesis could be a difference in elapsed time between diabetes onset and its diagnosis in type 2 diabetes compared with latent autoimmune diabetes. Although it is well known that patients with newly diagnosed type 2 diabetes have been exposed to the detrimental effects of hyperglycaemia for years before diagnosis,<sup>29</sup> this finding has never been demonstrated in patients with latent autoimmune diabetes. Theoretically, the presence of autoimmunity could also have accelerated the onset of overt diabetes. The subgroup analyses showing an initial lower risk of microvascular complications in participants with latent autoimmune diabetes with a higher autoimmune load (ie, those with more than one detectable autoantibody and those with high autoantibody titre) might in part support this hypothesis.

Results of this study might have relevant implications for the understanding of the differential risk of complications between type 2 diabetes and autoimmune diabetes in general. Because of the genetic predisposition, the presence of detectable autoantibodies and the reduced  $\beta$ -cell function, latent autoimmune diabetes is in fact often referred to as a misdiagnosed form of type 1 diabetes. Therefore, latent autoimmune diabetes could be the right bench test for studying differences between autoimmune diabetes and type 2 diabetes, because of fewer disparities in age and disease duration than with the comparison of type 1 diabetes and type 2 diabetes.<sup>30</sup> In this regard, this study is the first to evaluate the impact of  $\beta$ -cell function on the risk of retinopathy and nephropathy in latent autoimmune diabetes. The Diabetes Control and Complications Trial<sup>8</sup> clearly showed that preserved  $\beta$ -cell function at diabetes onset is associated with better microvascular outcomes in patients with type 1 diabetes. However, stratifying for baseline HOMA2-B did not alter the risk of microvascular complications in UKPDS

participants with latent autoimmune diabetes after adjustment for baseline features.

Strengths of this study include the largest population of patients with latent autoimmune diabetes with the longest follow-up studied in a randomised controlled trial so far, the adjudication of all microvascular events by the UKPDS endpoint committee, and a complete description of metabolic features at diabetes onset and for many years after diagnosis. Limitations of this study include the possibility of having included patients with adult-onset type 1 diabetes, which is unlikely as they comprise less than 5·5% of all autoantibody-positive patients; the possibility of having misclassified some of the 920 patients with one autoantibody measurement missing and whose other two autoantibody tests were negative as having type 2 diabetes, which also is unlikely as the prevalence of patients with latent autoimmune diabetes who were IA-2A positive was low;<sup>7</sup> the different recommendations concerning glycaemic targets and diabetes treatment options in UKPDS compared with current recommendations; the possibility that post-trial questionnaires used to identify potential UKPDS endpoints might not have captured all non-fatal outcomes; and the inability to estimate  $\beta$ -cell function with HOMA in patients taking insulin<sup>14</sup> and the high number of participants with latent autoimmune diabetes who required insulin within 9 years from the diagnosis<sup>2</sup> that precluded evaluation of the impact on the composite microvascular outcome of a probably sustained difference in  $\beta$ -cell function. Neuropathy could also not be examined here given the lack of an adjudicated composite neuropathy outcome in UKPDS. Finally, although we acknowledge that the biphasic risk pattern for the primary composite microvascular outcome was mainly driven by retinopathy events, the same pattern is observed for both retinopathy and nephropathy outcomes (albeit there are much fewer events for the latter).

In conclusion, measurement of diabetes-related autoantibodies helps in identifying patients with a clinical diagnosis of type 2 diabetes who in fact have latent autoimmune diabetes and whose initial lower risk of developing microvascular complications is reversed over time by sustained poorer glycaemic control. This evidence might allow tailored screening strategies and highlights the existence of an early therapeutic window in latent autoimmune diabetes to improve microvascular outcomes by implementing strict glycaemic control.

#### Contributors

EM designed the statistical plan, analysed and interpreted data, and wrote the manuscript. RLC extracted data, helped with the statistical plan, and revised the manuscript. OA helped with statistical analysis. RB helped with data interpretation and critically reviewed the manuscript. RRH designed the study, interpreted data, and critically reviewed the manuscript.

#### Declaration of interests

EM has received grants from scientific societies supported by Lilly and AstraZeneca and honoraria from Merck-Serono, Pikdare, AstraZeneca, and Abbott. RB has received honoraria or consulting fees from Sanofi, Eli Lilly, Abbott, and AstraZeneca. RRH has received grants from

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