Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91)

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Summary

Background The 20-year UK Prospective Diabetes Study showed major clinical benefits for people with newly diagnosed type 2 diabetes randomly allocated to intensive glycaemic control with sulfonylurea or insulin therapy or metformin therapy, compared with conventional glycaemic control. 10-year post-trial follow-up identified enduring and emerging glycaemic and metformin legacy treatment effects. We aimed to determine whether these effects would wane by extending follow-up for another 14 years.

Methods 5102 patients enrolled between 1977 and 1991, of whom 4209 (82·5%) participants were originally randomly allocated to receive either intensive glycaemic control (sulfonylurea or insulin, or if overweight, metformin) or conventional glycaemic control (primarily diet). At the end of the 20-year interventional trial, 3277 surviving participants entered a 10-year post-trial monitoring period, which ran until Sept 30, 2007. Eligible participants for this study were all surviving participants at the end of the 10-year post-trial monitoring period. An extended follow-up of these participants was done by linking them to their routinely collected National Health Service (NHS) data for another 14 years. Clinical outcomes were derived from records of deaths, hospital admissions, outpatient visits, and accident and emergency unit attendances. We examined seven prespecified aggregate clinical outcomes (ie, any diabetes-related endpoint, diabetes-related death, death from any cause, myocardial infarction, stroke, peripheral vascular disease, and microvascular disease) by the randomised glycaemic control strategy on an intention-to-treat basis using Kaplan–Meier time-to-event and log-rank analyses. This study is registered with the ISRCTN registry, number ISRCTN75451837.

Findings Between Oct 1, 2007, and Sept 30, 2021, 1489 (97·6%) of 1525 participants could be linked to routinely collected NHS administrative data. Their mean age at baseline was 50·2 years (SD 8·0), and 41·3% were female. The mean age of those still alive as of Sept 30, 2021, was 79·9 years (SD 8·0). Individual follow-up from baseline ranged from 0 to 42 years, median 17·5 years (IQR 12·3–26·8). Overall follow-up increased by 21%, from 66 972 to 80 724 person-years. For up to 24 years after trial end, the glycaemic and metformin legacy effects showed no sign of waning. Early intensive glycaemic control with sulfonylurea or insulin therapy, compared with conventional glycaemic control, showed overall relative risk reductions of 10% (95% CI 2–17; p=0·015) for death from any cause, 17% (6–26; p=0·002) for myocardial infarction, and 26% (14–36; p<0·0001) for microvascular disease. Corresponding absolute risk reductions were 2·7%, 3·3%, and 3·5%, respectively. Early intensive glycaemic control with metformin therapy, compared with conventional glycaemic control, showed overall relative risk reductions of 20% (95% CI 5–32; p=0·010) for death from any cause and 31% (12–46; p=0·003) for myocardial infarction. Corresponding absolute risk reductions were 4·9% and 6·2%, respectively. No significant risk reductions during or after the trial for stroke or peripheral vascular disease were observed for both intensive glycaemic control groups, and no significant risk reduction for microvascular disease was observed for metformin therapy.

Interpretation Early intensive glycaemic control with sulfonylurea or insulin, or with metformin, compared with conventional glycaemic control, appears to confer a near-lifelong reduced risk of death and myocardial infarction. Achieving near normoglycaemia immediately following diagnosis might be essential to minimise the lifetime risk of diabetes-related complications to the greatest extent possible.

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Introduction

Spanning over 20 years, the UK Prospective Diabetes Study (UKPDS)[1] was a randomised, multicentre trial among people with newly diagnosed type 2 diabetes. Findings from the UKPDS showed relative risk reductions with an intensive glycaemic control strategy with sulfonylurea or insulin therapy, compared with a conventional glycaemic control strategy (primarily with diet), of 12% for any diabetes-related endpoint (p=0·029) and 25% for clinically evident microvascular

Research in context

Evidence before this study

Literature searches before the initiation of this study in 2014 did not reveal any publications relating to legacy effects in people with type 2 diabetes. However, we searched PubMed from inception to April 12, 2024, using the search terms "type 2 diabetes", "legacy effect", and "systematic" for studies published only in English. We found one meta-analysis of three studies of which findings did not detect a legacy effect of more than 5-year intensive blood glucose control on cardiovascular outcomes in patients with type 2 diabetes and very high risk or secondary prevention of cardiovascular disease. A subsequent narrative review of seven randomised controlled trials in 2020 did not support the existence of a protective legacy effect on the macrovasculature beyond the period of intensive glycaemic treatment.

In 1998, the 20-year UK Prospective Diabetes Study (UKPDS) primary results were reported. They showed substantial risk reductions for the primary outcome of any diabetes-related endpoint and for clinically evident microvascular complications in people with newly diagnosed type 2 diabetes randomly assigned to an intensive glycaemic control strategy with sulfonylurea or insulin, compared with a conventional glycaemic control strategy. Participants with more than 120% of their ideal bodyweight randomly assigned to an intensive glycaemic control strategy with metformin, compared with a conventional glycaemic control strategy, saw substantial risk reductions for any diabetes-related endpoint, death from any cause, and for myocardial infarction.

In 2008, the 10-year UKPDS post-trial monitoring study results were reported. The post-trial monitoring study first identified major legacy effects of early intensive glycaemic control with sulfonylurea or insulin, and with metformin. Findings showed that the within-trial risk reductions for major clinical outcomes endured, or emerged anew as statistically significant, despite mean glycated haemoglobin (HbA_{1c}) values becoming no different between study groups by 1 year after trial end, and then decreasing progressively over time in both groups with increasing use of multiple glucose-lowering therapies. These legacy effects of earlier treatment might be akin to the metabolic memory effect first described in people with type 1 diabetes by the Epidemiology of Diabetes Interventions and Complications follow-up of the Diabetes Control and Complications Trial, and could well share similar mechanisms.

Added value of this study

Analyses performed after the addition of up to another 14 years of participant follow-up using routinely collected National Health Service administrative data demonstrate that the glycaemic and metformin legacy effects do not wane over time, as widely anticipated, but remain undiminished for up to 24 years after trial end. The continued benefits of minimising hyperglycaemia from the time of diagnosis of type 2 diabetes appear to lead to near-lifelong reduced risk of death and microvascular complications in participants randomly assigned to sulfonylurea or insulin therapy, and to reduced risk of death and myocardial infarction in those assigned to metformin therapy.

Implications of all the available evidence

These UKPDS findings further emphasise the importance of achieving near normoglycaemia as soon as people are diagnosed with type 2 diabetes to minimise the lifetime risk of diabetes-related complications to the greatest extent possible.

complications (p=0·0099).[1] The 16% relative risk reduction for myocardial infarction did not achieve conventional statistical significance (p=0·052). In participants with more than 20% of their ideal bodyweight (which equates approximately to a BMI of >27 kg/m²),[2] relative risk reductions with an intensive glycaemic control strategy with metformin, compared with a conventional glycaemic control strategy, were 32% for any diabetes-related endpoint (p=0·0023), 36% for death from any cause (p=0·01), and 39% for myocardial infarction (p=0·01).[3]

Following trial end in 1997 with cessation of the randomised treatment strategies, all surviving participants entered a 10-year post-trial monitoring study and were returned to community-based or hospital-based diabetes care according to their clinical needs. The post-trial monitoring study identified glycaemic and metformin legacy effects, whereby risk reductions for major clinical outcomes endured, or emerged as statistically significant.[4] Previous randomisation to an intensive glycaemic control strategy with sulfonylurea or insulin, compared with a conventional glucose control strategy, resulted in overall relative risk reductions of 13% for death from any cause (p=0·007), 15% for myocardial infarction (p=0·01), and 24% for microvascular disease (p=0·001). Previous randomisation to an intensive glycaemic control strategy with metformin, compared with a conventional glycaemic control strategy, resulted in overall relative risk reductions of 21% for any diabetes-related endpoint (p=0·01), 27% for death from any cause (p=0·002), and 33% for myocardial infarction (p=0·005). These legacy effects occurred despite no attempts being made to maintain people on their previously randomly allocated treatment strategies, and despite mean glycated haemoglobin (HbA_{1c}) values becoming similar between groups within 1 year after trial end, and then becoming progressively lower over the next 4 years.[4] During the same period, the number and intensity of glucose-lowering therapies increased in both groups, with no discernible differences at 5 years.[4] Successful community-based efforts to improve HbA_{1c} values and greater use of glucose-lowering agents possibly reflect the issuing of more aggressive clinical guidelines for managing

glycaemia, informed by the UKPDS findings. For instance, in the US National Health and Nutrition Examination Survey, the proportion of people with HbA_{1c} values of less than 7·0% increased from 37% in the year 1999–2000 to 57% in the year 2003–04.[5]

To determine the degree to which post-trial glycaemic and metformin legacy effects would wane over time, we extended post-trial monitoring for another 14 years using routinely collected UK National Health Service (NHS) administrative data.

Methods

Study design and participants

UKPDS patient recruitment, study protocol, and methods have been previously reported.[1,3,6] Ethics committees at all 23 clinical centres in the UK approved the trial, which conformed to the Declaration of Helsinki guidelines. The 5102 patients enrolled between 1977 and 1991, aged 25–65 years with a median age of 53 years (IQR 46–59), provided written informed consent. Of these patients, 3867 were randomly assigned to receive intensive glycaemic control (sulfonylurea or insulin) or conventional glycaemic control (diet); in addition, 342 participants with more than 20% of their ideal bodyweight (which equates approximately to a BMI of >27 kg/m²) were randomly assigned to receive intensive glucose control with metformin and compared with 411 participants who were overweight in the conventional glucose control group (figure 1).

When the 20-year interventional trial ended on Sept 30, 1997, all 3277 surviving participants provided written informed consent to enter a 10-year post-trial monitoring study, which ran until Sept 30, 2007.[4] These participants returned to usual community-based or hospital-based care, with no attempt made to maintain previously randomised treatment strategies. For the first 5 years, where feasible, participants were seen annually in UKPDS clinics with standardised outcome data

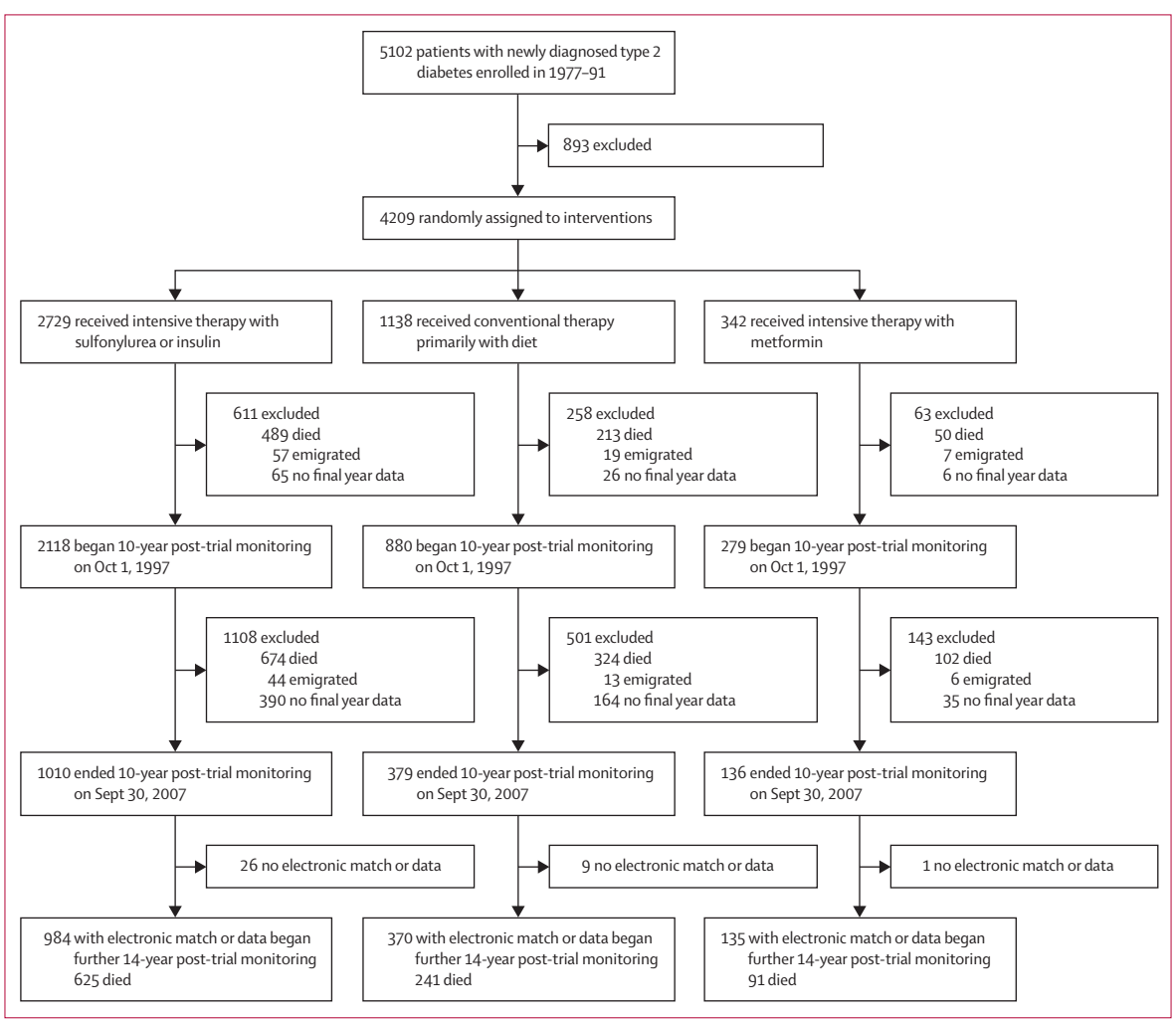

Figure 1: **Trial profile**
The 10-year post-trial monitoring period took place between Oct 1, 1997, and Sept 30, 2007, and the further 14-year post-trial monitoring period took place between Oct 1, 2007, and Sept 30, 2021.

collection, and a clinical examination every 3 years. For those unable to attend UKPDS clinics during this period, and for all participants for the subsequent 5 years, questionnaires to participants and their general practitioners were used to continue follow-up remotely. UKPDS Endpoint Committee members continued to adjudicate outcomes exactly as they had during the interventional trial. The eligible participants for this study were all surviving participants at the end of the 10-year post-trial monitoring period.

NHS administrative data

We extended follow-up of all participants alive at the end of the post-trial monitoring study by linking them, where possible, to their routinely collected NHS data for another 14 years from 2007 to 2021 with ethical approval (South East Scotland REC 01,18/SS/0127). Linkage was done using UKPDS participant NHS numbers, sex, date of birth, postcode, and first and last names. We sought participant data from NHS England Digital for the 19 English centres, from Public Health Scotland for the two Scottish centres, and from the General Registry Office of Northern Ireland (GRONI) and the Northern Ireland Electronic Care Record for the two Northern Ireland centres. These databases record health outcomes collected during usual NHS universal health care using the International Classification of Disease (ICD) codes versions 9 and 10. Clinical outcomes were derived from records of deaths, hospital admissions, hospital outpatient visits, and accident and emergency unit attendances. We included data on deaths and cause of death from the Office for National Statistics. The GRONI electronic death records could not be exported to England, so they were searched in person in Belfast by AIA and WNW.

We mapped ICD-10 event codes to the 21 prespecified clinical endpoints defined in the UKPDS protocol (appendix p 3).[6] We considered any ICD-10 codes reflecting a UKPDS outcome listed anywhere on the discharge summary or outpatient record.[7] To assign cause of death, we used the cause listed in the primary position on UK death certificates (Part 1a),[8] unless the participant had been admitted to hospital within 28 days when we assigned the complication of diabetes recorded at hospital discharge as the cause of death.

See Online for appendix

UKPDS aggregate clinical outcomes

Seven UKPDS predefined aggregate clinical outcomes were assessed. These outcomes comprised the following: any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, fatal or non-fatal stroke, renal death, renal failure, death from peripheral vascular disease, amputation, vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (sudden death or death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia, or hypoglycaemia); death from any cause; myocardial infarction (sudden death or fatal or non-fatal myocardial infarction); stroke (fatal or non-fatal stroke); peripheral vascular disease (lower extremity amputation of at least one digit, or death from peripheral vascular disease); and microvascular disease (vitreous haemorrhage, retinal photocoagulation, renal death, or renal failure). We did not have access to measures of glycaemia or blood pressure, or data on pharmacological treatments.

Statistical analysis

We did analyses according to the intention-to-treat principle, presenting descriptive statistics as numbers and percentages or appropriate measures of central tendency and dispersion. We defined baseline as the time of randomisation into the interventional trial. For fatal events, we calculated time from baseline to death or to censoring. We assumed that all deaths were recorded, and that participants successfully linked to NHS records who had no death reported were alive on Sept 30, 2021 (24 years from trial end) and censored them at that time. For non-fatal events, we calculated time from baseline to the first occurrence of an event or to censoring. We censored participants who were alive and complication-free as of March 31, 2021 (limit of available NHS data), or who had died, or who were lost to follow-up during the interventional trial or post-trial monitoring study. We considered participants as lost to follow-up at the end of the post-trial monitoring study if they were alive, but could not be linked to NHS data. Missing data were not imputed. Before performing our analyses, we did Kaplan–Meier plots from baseline by randomised strategy groups for all data for each aggregate outcome to examine whether event accrual remained proportionate over time following the addition of endpoints derived from NHS administrative data.

Our primary question was the degree to which the glycaemic or metformin legacy effects, or both, identified in the 10-year post-trial monitoring study would wane over time. We did Kaplan–Meier time-to-event analyses from baseline for each aggregate clinical outcome, using log-rank tests for differences between randomised glycaemic control strategies. To illustrate possible waning in relative risks during the additional 14 years of follow-up from Oct 1, 2007, we used cumulative hazard ratio (HR) plots with 95% CIs, but calculated p values only for the final year of follow-up, as was done for the 10-year follow-up analyses to avoid multiple testing.[4] We did not test for differences in HRs over time; we did test proportional hazards assumptions using log-log survival curves by randomised glycaemic control strategies and by modelling hazard rates. Absolute risk rates were expressed as the number of events per 1000 patient-years. We considered p values less than 0·05 as significant and did not adjust for multiple analyses.

We did all statistical analyses using SAS (version 9.4). This trial is registered with the ISRCTN registry, number ISRCTN75451837.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1525 participants were alive at the end of the 10-year post-trial monitoring study (figure 1). Of these, 1489 (97·6%) could be linked to routinely collected NHS administrative data. Their mean age at baseline was 50·2 years (SD 8·0), and 41·3% were female. Their mean age at the start of administrative follow-up was 70·9 years (SD 8·5), and the mean age of those still alive as of Sept 30, 2021, was 79·9 years (SD 8·0). We collected mortality data for the 130 Northern Ireland participants, but approval to use non-fatal clinical event data could not be obtained in the absence of a functioning Northern Ireland Assembly.[9] Baseline mean age and sex proportions did not differ between those who could or could not be linked to administrative data (appendix p 4). Kaplan–Meier plots from baseline for the seven aggregate outcomes showed that endpoint ascertainment over time remained proportionate following the addition of endpoints derived from routinely collected NHS administrative data (appendix pp 5–6).

As of Sept 30, 2021, 2809 (66·7%) of 4209 participants allocated to an intensive glycaemic control strategy (with sulfonylurea or insulin therapy or metformin therapy) or to a conventional glycaemic control strategy had died (figure 1). Mean age of those still alive was 79·9 years (SD 8·0). Individual follow-up from baseline ranged from 0 to 42 years, median 17·5 years (IQR 12·3–26·8). Overall follow-up increased by 21% from 66 972 to 80 724 person-years. The median follow-up time from baseline in the sulfonylurea or insulin group was 17·3 years (IQR 12·3–27·1) and in the metformin group was 19·1 years (14·0–28·4). The follow-up times for the corresponding conventional glycaemic control groups were 17·4 years (IQR 12·1–25·4) and 17·6 years (12·3–24·3), respectively. These follow-up times equated to 73 667 person-years for the sulfonylurea or insulin group and corresponding conventional glycaemic control group, and 14 716 person-years for the metformin group and corresponding conventional glycaemic control group, of which NHS administrative data contributed 12 561 (17·1%) and 2285 (15·5%) person-years, respectively.

The glycaemic legacy effects seen during the post-trial monitoring study in the sulfonylurea or insulin intensive therapy group, compared with the conventional therapy group, did not wane over the following 14 years. Over time, the separation of the Kaplan–Meier plot curves did not diminish (figure 2; appendix p 7), and the cumulative HRs appeared to remain constant (figures 3–4).

After adding routinely collected NHS administrative follow-up data, the overall relative risk reductions from baseline seen in the sulfonylurea or insulin group were 10% (95% CI 2–17; p=0·015) for death from any cause, 17% (6–26; p=0·002) for myocardial infarction, and 26% (14–36; p<0·0001) for microvascular disease (table; figures 2–3). Corresponding absolute risk reductions were 2·7%, 3·3%, and 3·5%, respectively. We observed no significant risk reductions during or after the trial for stroke or peripheral vascular disease (table).

The metformin legacy effects seen during the post-trial monitoring study in the metformin group, compared with the conventional-therapy group, did not wane over the following 14 years. Over time, the separation of the Kaplan–Meier plot curves did not diminish (figure 2; appendix p 7), and the cumulative HRs appeared to remain constant (figures 3–4).

Following the addition of the routinely collected NHS administrative follow-up data, the overall relative risk reductions from baseline in the metformin group were 20% (95% CI 5–32; p=0·010) for death from any cause and 31% (12–46; p=0·003) for myocardial infarction (table). Corresponding absolute risk reductions were 4·9% and 6·2%, respectively. We observed no significant risk reductions during or after the trial for stroke, peripheral vascular disease, or microvascular disease (table).

We did not compare the HRs formally between the sulfonylurea or insulin group and metformin group, as we could only compare them directly in the overweight group, rather than overall. An indirect comparison in the whole population would be problematic because of the overlapping conventional therapy subgroups and bodyweight differences.

Discussion

This follow-up of UKPDS participants for up to 42 years is perhaps the longest for any clinical trial to date,[10] with more than 80 000 person-years accrued. Following up to 14 more years of post-trial monitoring using routinely collected NHS administrative data, analyses show that the previously identified glycaemic and metformin legacy effects[4] do not wane for up to 24 years after the trial ended. The legacy benefits from early intensive glycaemic control with sulfonylurea or insulin led to overall relative risk reductions from baseline of 10% for death, 17% for myocardial infarction, and 26% for microvascular complications. Early intensive glycaemic control with metformin led to numerically larger overall relative risk reductions than with sulfonylurea or insulin, from baseline of 20% for death and 31% for myocardial infarction. These landmark findings emphasise the importance of achieving good glycaemic control for people with type 2 diabetes as early as possible. By contrast, the substantial within-trial relative risk reductions seen with tight blood pressure control in the UKPDS[11] waned rapidly during the post-trial monitoring study, with all HRs moving towards unity.[12]

The pathophysiological mechanisms responsible for persisting glycaemic and metformin legacy effects remain unclear. Perhaps the glycaemic legacy effect is in reality a hyperglycaemic legacy effect, whereby initial poor glycaemic control induces irreversible pathophysiological changes, permanently increasing the

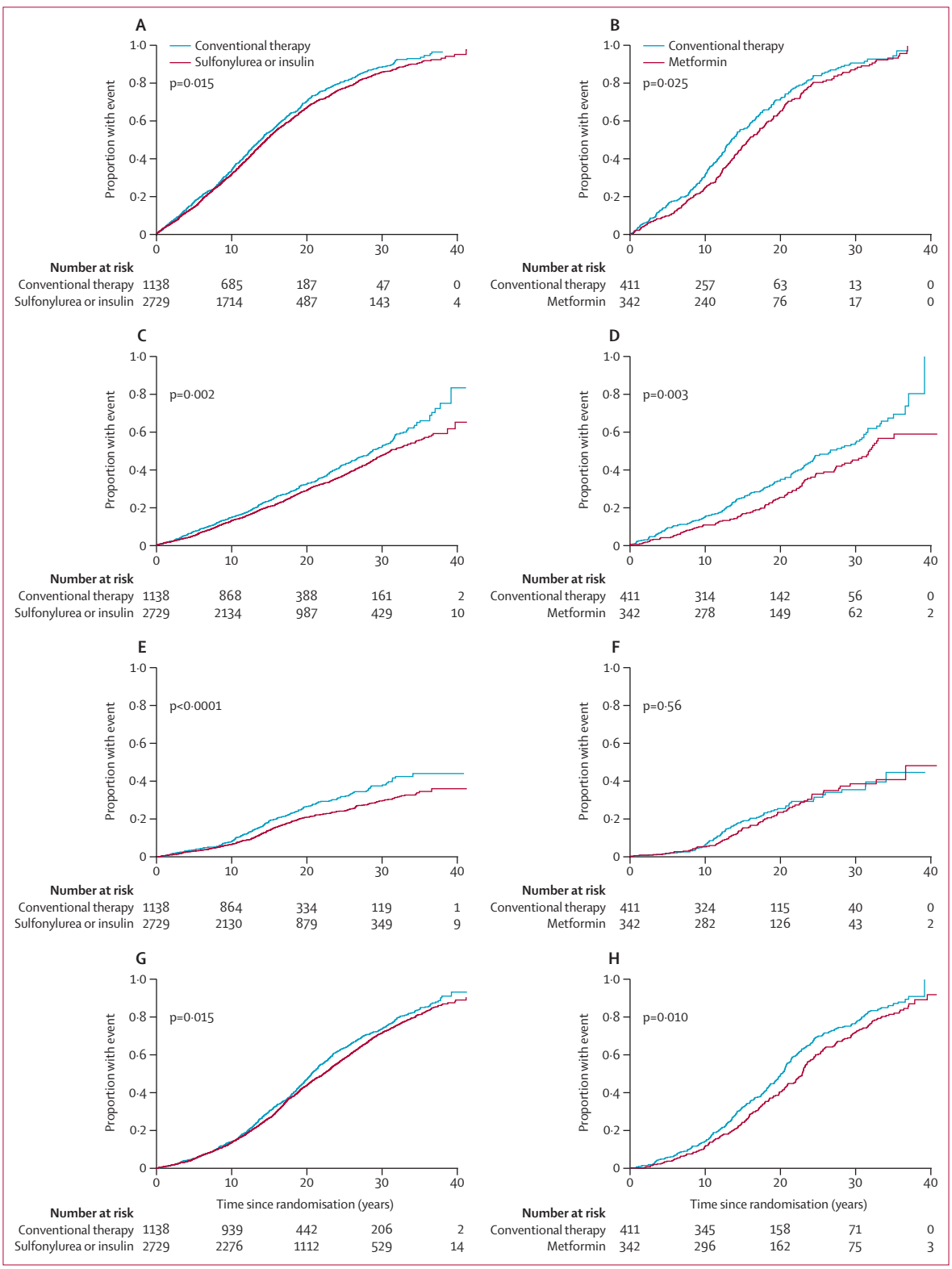

Figure 2: **Kaplan–Meier curves for four prespecified aggregate clinical outcomes**
The proportions of the UK Prospective Diabetes Study participants who had any diabetes-related endpoint (A–B), myocardial infarction (C–D), microvascular disease (E–F), or who died from any cause (G–H) are shown for the sulfonylurea or insulin group and for the metformin group, respectively vs their corresponding conventional therapy groups. Plots show cumulative incidence with numbers at risk at 10-year intervals from baseline, truncated at 40 years as so few participants remained at risk. Log-rank p values are shown for the entirety of follow-up. Kaplan–Meier curves for the other three prespecified aggregate clinical outcomes are summarised in the appendix (p 7).

risks of diabetes-related complications and death. Post-hoc UKPDS analyses have shown that glycaemic legacy effects can be explained predominately by historical HbA_{1c} values having a greater risk impact than more recent values.[13] Each percentage point higher HbA_{1c} value seen 20 years before death confers a 36% increased

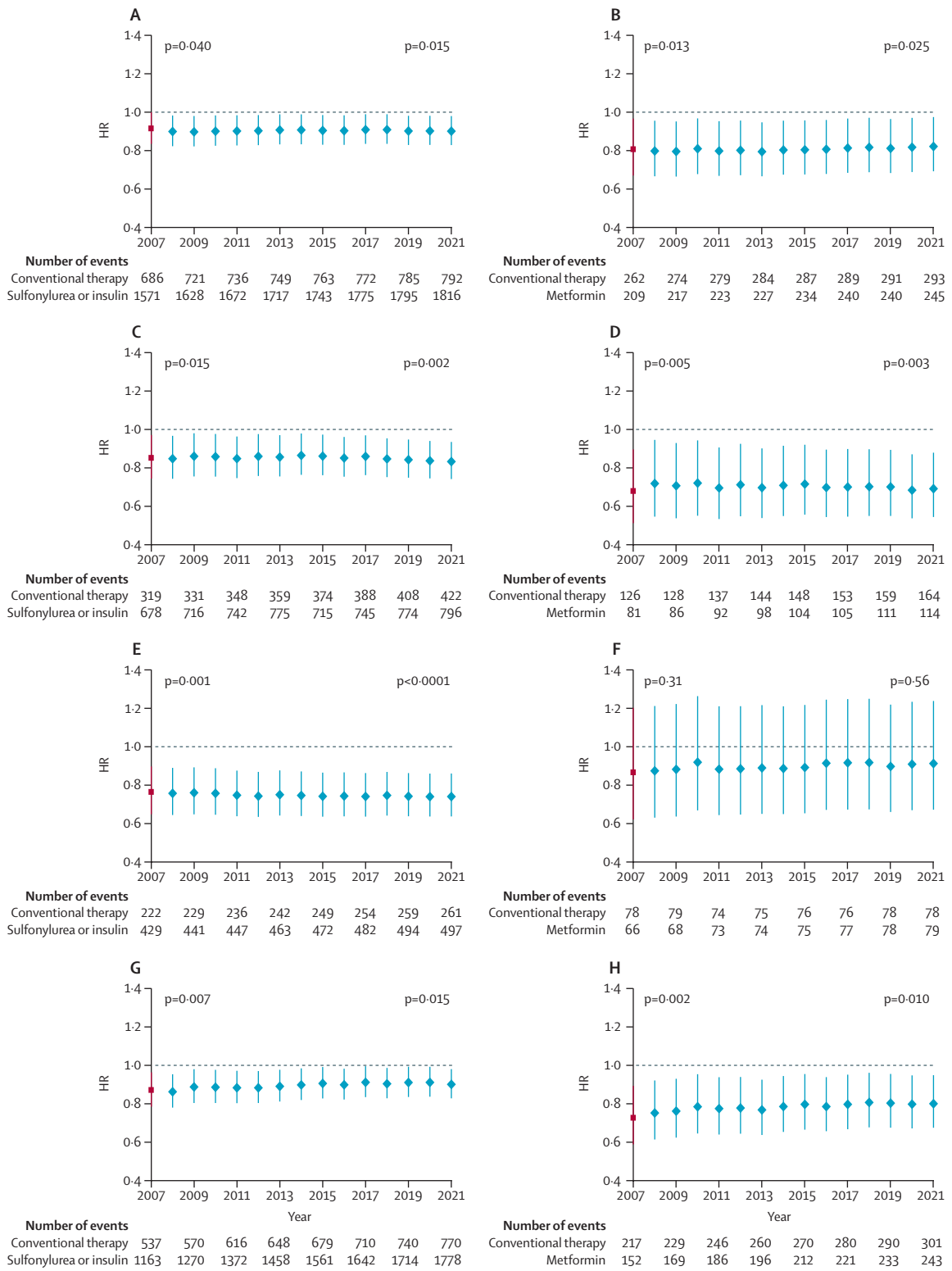

Figure 3: **HRs for four prespecified aggregate clinical outcomes**
HRs for the UK Prospective Diabetes Study participants who had any diabetes-related endpoint (A–B), myocardial infarction (C–D), microvascular disease (E–F), or who died from any cause (G–H) are shown for the sulfonylurea or insulin group and for the metformin group, respectively *vs* their corresponding conventional therapy groups. The red squares show the overall values at the end of the 10-year post-trial monitoring period in 2007.[4] The blue diamonds show the annual values during the National Health Service administrative data 14-year follow-up. HRs below unity indicate a favourable outcome from sulfonylurea or insulin therapy or metformin therapy. Numbers of first events in an aggregate outcome that accumulated in each group are shown at 2-year intervals. Error bars are 95% CIs. The dashed line shows a HR of 1, indicating no difference in time to event between the two groups. p values are shown for 2007 and 2021. HR=hazard ratio.

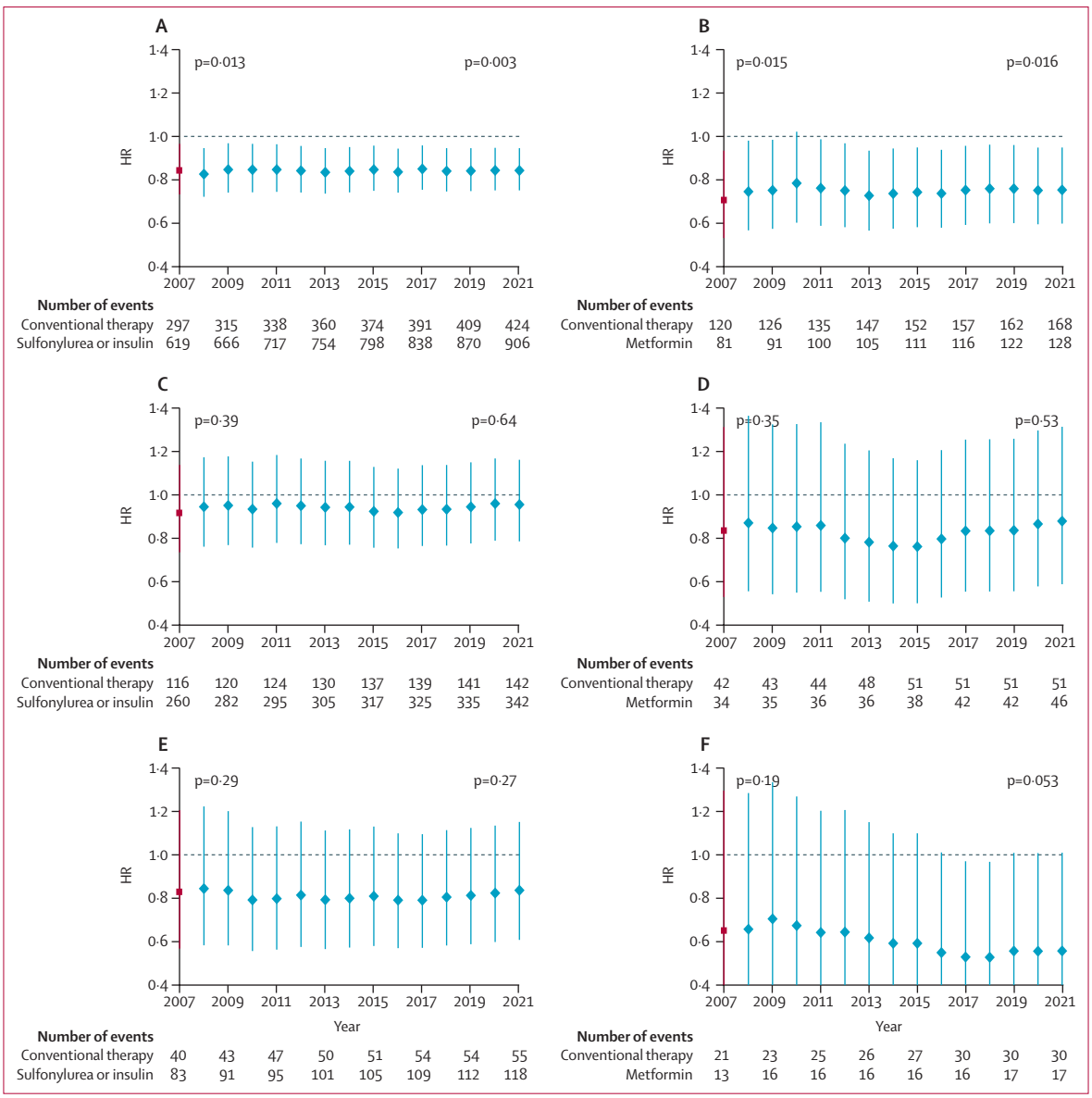

Figure 4: **HRs for three prespecified aggregate clinical outcomes**
HRs for participants in the UK Prospective Diabetes Study who had diabetes-related deaths (A–B), stroke (C–D), or peripheral vascular disease (E–F) are shown for the sulfonylurea or insulin group and for the metformin group, respectively *vs* their corresponding conventional therapy groups. The red squares show the overall values at the end of the 10-year post-trial monitoring period in 2007.[4] The blue diamonds show the annual values during the National Health Service administrative data 14-year follow-up. HRs below unity indicate a favourable outcome from sulfonylurea or insulin therapy or metformin therapy. Numbers of first events in an aggregate outcome that accumulated in each group are shown at 2-year intervals. Error bars are 95% CIs. The dashed line shows a HR of 1, indicating no difference in time to event between the two groups. p values are shown for 2007 and 2021. HR=hazard ratio.

relative risk for death, compared with just 8% for such values seen just 5 years before death. Simulated 20-year treatment scenarios showed that delaying a 1% HbA_{1c} decrease for 10 years, compared with an immediate decrease, would mean a drop in the estimated relative risk reduction for death from 18·6% to 6·6%. An observational study using the Kaiser Permanente Northern California Diabetes Registry data has shown that for patients with newly diagnosed type 2 diabetes who survived for at least 10 years, HbA_{1c} values of 6·5% or more (≥48 mmol/mol) for the first year after diagnosis, compared with less than 6·5% (<48 mmol/mol), were associated with worse outcomes.[14]

The glycaemic legacy effect first described by the UKPDS[4] is akin to the metabolic memory first described in people with type 1 diabetes by the Epidemiology of Diabetes Interventions and Complications[15] follow-up of the Diabetes Control and Complications Trial.[16] The type 2 diabetes legacy effect and the type 1 diabetes metabolic memory effect might share similar mechanisms.

	Participants with clinical outcome		Absolute risk		24-year post-trial follow-up		10-year post-trial follow-up	
	Intensive therapy	Conventional therapy	Intensive therapy	Conventional therapy	Relative risk for intensive therapy regimen (95% CI)	p value	Relative risk for intensive therapy regimen (95% CI)	p value
Sulfonylurea or insulin group								
Any diabetes-related endpoint	1816/2729 (66·5%)	792/1138 (69·6%)	50·4	54·9	0·90 (0·83–0·98)	0·015	0·91 (0·83–0·99)	0·040
Diabetes-related death	908/2729 (33·3%)	424/1138 (37·3%)	17·4	20·0	0·84 (0·75–0·94)	0·003	0·83 (0·73–0·96)	0·013
Death from any cause	1793/2729 (65·7%)	778/1138 (68·4%)	34·1	36.7	0·90 (0·83–0·98)	0·015	0·87 (0·79–0·96)	0·007
Myocardial infarction	897/2729 (32·9%)	422/1138 (37·1%)	18·4	21·7	0·83 (0·74–0·94)	0·002	0·85 (0·74–0·97)	0·015
Stroke	343/2729 (12·6%)	142/1138 (12·5%)	6·8	7·0	0·95 (0·78–1·16)	0·64	0·91 (0·73–1·13)	0·39
Peripheral vascular disease	118/2729 (4·3%)	55/1138 (4·8%)	2·3	2·7	0·83 (0·61–1·15)	0·27	0·82 (0·56–1·19)	0·29
Microvascular disease	497/2729 (18·2%)	261/1138 (22·9%)	10·7	14·2	0·74 (0·64–0·86)	<0·0001	0·76 (0·64–0·89)	0·001
Metformin group								
Any diabetes-related endpoint	245/342 (71·6%)	293/411 (71·3%)	49·6	56·2	0·82 (0·69–0·98)	0·025	0·79 (0·66–0·95)	0·013
Diabetes-related death	128/342 (37·4%)	168/411 (40·9%)	18·1	21.9	0·75 (0·60–0·95)	0·016	0·70 (0·53–0·92)	0·015
Death from any cause	243/342 (71·1%)	301/411 (73·2%)	34·4	49.3	0·80 (0·68–0·95)	0·010	0·73 (0·59–0·89)	0·002
Myocardial infarction	114/342 (33·3%)	164/411 (39·9%)	17·3	23·4	0·69 (0·54–0·88)	0·003	0·67 (0·51–0·89)	0·005
Stroke	46/342 (13·5%)	51/411 (12·4%)	6·7	7·0	0·88 (0·59–1·31)	0·53	0·80 (0·50–1·27)	0·35
Peripheral vascular disease	17/342 (5·0%)	30/411 (7·3%)	2·5	4·1	0·55 (0·31–1·01)	0·053	0·63 (0·32–1·27)	0·19
Microvascular disease	79/342 (23·1%)	88/411 (21·4%)	12·7	13·2	0·91 (0·67–1·24)	0·56	0·84 (0·60–1·17)	0·31

Data are n/N (%), unless otherwise specified. Absolute risk is the number of events per 1000 patient-years. Relative risk was estimated from hazard ratios calculated from proportional hazards modelling. p values were calculated using the log-rank test.

Table: **Clinical outcomes from baseline for participants after up to 24-year post-trial follow-up, and after up to 10-year post-trial follow-up, as previously reported[4]**

Proposed mechanisms include increased intracellular formation of advanced glycation end products, oxidative stress, and epigenetic changes enhancing expression of proinflammatory genes.[17,18] UKPDS has shown that establishing and maintaining near normoglycaemia from the time of diagnosis of type 2 diabetes minimises the risk of complications and prolongs life, and early metformin therapy reduces the risk of complications and of dying. The numerically greater magnitude of the metformin legacy effect suggests additional metformin-related protective mechanisms might exist, such as inhibition of the inflammatory pathway.[19]

Modern management of type 2 diabetes includes the use of newer glucose-lowering agents that have been shown to reduce the risk of diabetes-related complications such as GLP-1 receptor agonists[20] and SGLT2 inhibitors.[21] However, their glucose lowering properties appear to explain only part of their ability to prevent or delay cardiovascular and kidney diseases, suggesting that non-glycaemic mechanisms might largely be responsible.[22–26] We support the major role GLP-1 receptor agonists and SGLT2 inhibitors have in helping to reduce the risk of the complications of diabetes, but would emphasise the importance of avoiding hyperglycaemia however this outcome is achieved. Notably, all the therapies used in the UKPDS are off patent, have been shown previously to be cost-effective or indeed cost-saving,[27] are widely available globally at low cost, and are on the WHO List of Essential Medicines. The glycaemic legacy effect is likely to strengthen the economic case for the use of these therapies in low-income settings, as this study has demonstrated additional enduring health benefits long beyond the trial period.

Our study has some limitations. Additional clinical event data could be obtained only for participants who could be linked to routinely collected NHS administrative data, and we could not obtain non-fatal clinical event data for the 130 participants in the two Northern Ireland centres. However, because of the similar patterns of death across the three nations, we believe that had we obtained the Northern Ireland non-fatal event data our conclusions would not have changed. During this extended follow-up period, we did not have access to information about biochemical measures, including HbA_{1c} and plasma creatinine values, nor information about pharmacotherapy. Most participants not randomly assigned to the metformin group will likely have received this medication over time, suggesting that the true relative risk reductions for metformin could be even greater than we report. Non-fatal events that did not require admission to hospital or an outpatient procedure, for example blindness in one eye, might not have been captured. Events identified via routinely collected NHS administrative data could not be adjudicated, although a post-hoc analysis of the ASCEND trial suggests that routinely collected UK hospital admission and death registry data can be used as the sole method to follow up cardiovascular outcomes in primary prevention cardiovascular trials without needing to verify them by clinical adjudication.[28] Nevertheless, any misclassification of outcomes is unlikely to be related to previous randomisation. The number of participants (n=753) in

the metformin comparison is small by modern trial standards, but sufficient to show the differences in complication risks of the magnitude we report. This sample size was also nearly five times greater than the 160 participants in the highly regarded Steno-2 study, which first showed the beneficial effects of multifactorial intervention on morbidity[29] and later on mortality in type 2 diabetes.[30] As in previous UKPDS papers, no statistical adjustment was made for multiple testing of aggregate outcomes, and the dwindling cohort size secondary to mortality potentially limits the ability to detect new treatment-related differences. Competing risk methods were not used as cause-specific hazard models are appropriate when addressing aetiological questions.[31]

In conclusion, our results demonstrate near-lifelong legacy effects of early intensive glycaemic control with sulfonylurea or insulin and with metformin. Achieving near-normal glycaemia immediately after type 2 diabetes is diagnosed appears to be essential to minimise the lifetime risk of diabetes-related complications to the greatest extent possible.

Contributors

AIA, WNW, and RRH designed the study. AIA and RLC collected the Northern Ireland administrative data for deaths, which was ICD-10 coded by AIA and WNW. RLC and JL did the statistical analyses. RRH wrote the first draft of the manuscript. All authors contributed to preparation of the final submitted version of the manuscript, assume responsibility for the accuracy, had permission to access the raw data, and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Investigators wishing to access these data need to have a contract with NHS England and NHS Scotland, to obtain the relevant ethical and data governance permissions, and to have an analysis environment compliant with the Data Security and Protection Toolkit. Other data from this study (code lists and statistical code) are available. If costs for further data extraction and analyses can be covered, tabular data can be shared with collaborators by application to the UK Prospective Diabetes Study.

For the **Data Security and Protection Toolkit** see https://www.dsptoolkit.nhs.uk/

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