UKPDS 44 Years of Follow Up Legacy

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Background

The UKPDS 33 years study shown that intensive glucose arm significantly reduces microvascular complications over a 10-year duration in patients with less than 6 years newly diagnosed (T2DM) diabetes [1]. Overall, there was a good reduction towards macrovascular complications in this duration but did not reach statistically level. The patients were followed up additionally 10 years and later in 1997 the study was published. The microvascular benefits were still statistically significant after another 10 years despite the intensive group's glycaemic control deteriorating in the later years to approach the control group's glycaemic control. This is often labelled as the "legacy effect". Further, after the subsequent 10 years, macrovascular benefits became statistically significant. It's been 44 years since the participants started in the study back in 1977. A preliminary report on the 44-year outcomes was presented recently at the EASD 2022 in Stockholm.

We are so used to quoting from the UKPDS study for so long now that it might be prudent to revisit the original UKPDS study details before we dive into the 44-year follow up report. I always thought that there were two groups – the intensive glucose intervention arm vs the conventional care arm. In fact, they had 3 groups – the intensive glucose intervention group utilising sulphonyl-urea (SI)and/or insulin, another intensive glucose intervention group utilising metformin and the conventional care group. (see Figure 1). The **final results** were always reported as the intensive group(s) combining the SU/insulin data with the metformin data. It is insightful to tease out the differences between the two intensive groups.

Figure 1: Trial Group
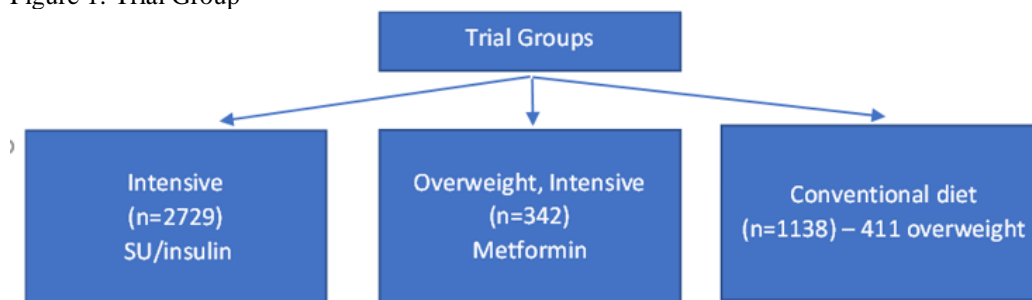
Legacy of 44 Follow UP of UKPDS

Interestingly, the often quoted "intensive blood glucose lowering significantly lower the risk of microvascular complications but had non-significant lowering of macrovascular complications" primarily relates to intensive control with SU/insulin. When we look at intensive glucose control with metformin group, the microvascular complications were not significant but the macrovascular benefits were. Because the number of participants in the metformin group were small, the effect was diluted in the overall **composite data** analysis. Further, the reduction **in all-cause mortality** was statistically significant in the metformin but not in the SU/insulin group.

After the intervention was completed and the intervention ended in 1997, the participants were monitored for another 10 years. The follow up study was published in 2007. While the glucose control was better in the intensive glucose control group compared with the conventional group in the first 10 years of the study, the difference in glucose control between groups were lost as the conventional group improved and the intensive group deteriorated over the years. All diabetes endpoints continue to be better in the intensive group despite a deterioration in their glucose control in subsequent years. That is often referred to as the "**legacy effect**".

The post-trial monitoring did not end in 2007. Participants continued to be monitored for another 14 years (see Figure 2). Data were collected from the NHS Digital which primarily consist of hospital admissions, outpatient

appointments, attendance at accident and emergency departments and deaths. It did not include any primary care data. Only data from England were presented as they await data from Scotland and Northern Ireland.

They compared groups that were previously allocated – SU/Insulin vs conventional and Metformin vs conventional groups. They compared 4 **aggregate complications of diabetes** (any diabetes-related endpoints, all-cause mortality, myocardial infarction and microvascular complications), health economics and all-cause dementia between the groups.

Figure 2. After 44 years of UKPDS Follow UP

Despite the passage of time and the similarities in their glycaemic control after the first 10 years, when they looked at **any diabetes-related endpoint**, there was still a statistically significant 10 % reduction in the SU/Insulin group compared to conventional group. When they looked at AMI specifically, they had a statistically significant 15% reduction in the SU/insulin arm versus with the standard arm. Similarly, there was a significant 26% reduction in microvascular complications between the two arms. All-cause mortality was also better by 11% in the SU/Insulin group compared to conventional arm. The difference between groups were pretty much similar to those back in 1997 and 2007 suggesting the benefits were maintained with the exception of all-cause mortality which was not significant in the original 1997 report.

Remarkably, the benefits of metformin vs conventional care were very similar to the benefits of SU/Insulin over conventional care except for microvascular complications where metformin **did not** have any significant benefits over the conventional group. However, the **all-cause mortality** benefit of metformin which was present even after 10 years were maintained into the 44th year.

Figure 3: UKPDS 44 years of Timeline
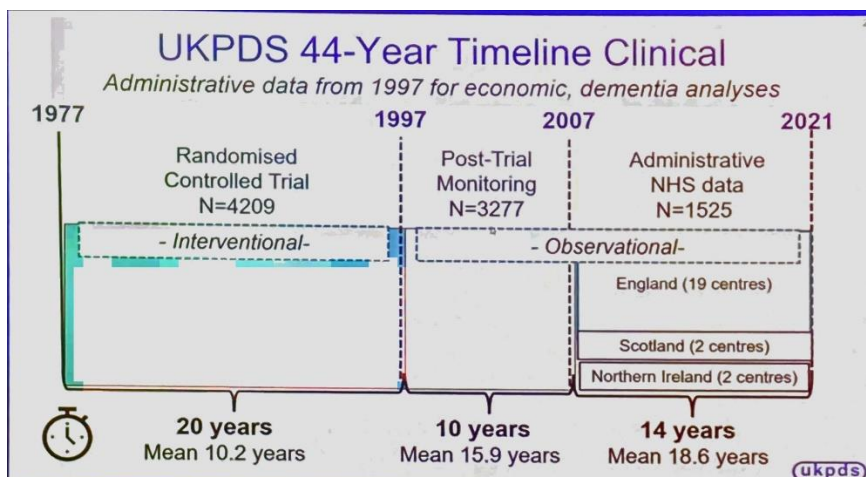
Credit: UKPDS Group

Legacy effect according to HbA1c

Compared with a 50-year-old patient whose HbA1c was left at 8% for the first 20 years, the same patient whose HbA1c was 8% for the first 10 years but was reduced to 7% for the subsequent 10 years, there was a 6.6% relative risk reduction (RRR) in death. If that patient had the HbA1c reduced to 7% right at the start and kept < 7.0% for the next 20 years, there was a 18.6% reduction in RRR! (see Figure 4).

Figure 4: Relative Reduction of Death

Credit: UKPDS Group

Table 1: The Persistence of Microvascular Benefits in SU/Insulin Group

Impact of Intensive Glucose Control with Sulfonylurea/Insulin

Aggregate Endpoint		Median Follow-up		
		10.0y 1997	16.9y 2007	17.4y 2021
Any diabetes-related endpoint	RRR:	12%	9%	10%
	P:	0.029	0.040	0.016
Myocardial infarction	RRR:	16%	15%	15%
	P:	0.052	0.014	0.0074
Microvascular disease	RRR:	25%	24%	26%
	P:	0.0099	0.001	<0.0001
All-cause mortality	RRR:	6%	13%	11%
	P:	0.44	0.007	0.0093

RRR = Relative Risk Reduction, P = Log Rank

UKPDS 33 Lancet 1998;352:837-853. UKPDS 80. N Engl J Med 2008;359:1577-89. Unpublished data (ukpds)

Life expectancy gains including QALYs gained

The phrase "quality-adjusted life year" or "QALY" measures health outcomes related to disease load and is used to assess the value of medical treatment. Health is defined by both the length and quality of life, and the QALY combines these factors into a single figure.

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QALYs gained additional years or months in terms of quality of time following the treatment given to individual, which indicator of significance in recent years specially with Chronic conditions as diabetes

Table 2: Persistence of MI and All-cause Mortality reduction with Metformin benefits across the Time

Impact of Intensive Glucose Control with Metformin

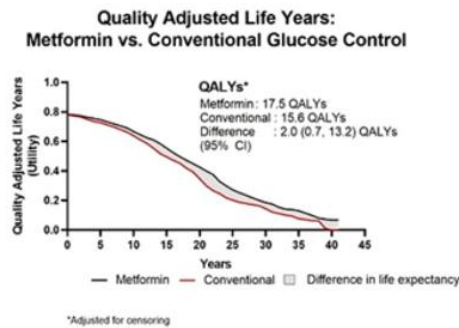| | | Median Follow-up | | |
Aggregate Endpoint		10.7y 1997	17.7y 2007	18.0y 2021
Any diabetes-related endpoint	RRR:	32%	21%	19%
	P:	0.0023	0.013	0.015
Myocardial infarction	RRR:	39%	33%	31%
	P:	0.010	0.005	0.0037
Microvascular disease	RRR:	29%	16%	10%
	P:	0.19	0.31	0.49
All-cause mortality	RRR:	36%	27%	25%
	P:	0.011	0.002	0.002

RRR = Relative Risk Reduction, P = Log Rank

UKPDS 33 Lancet 1998;352:837-853. UKPDS 80. N Engl J Med 2008;359:1577-89. Unpublished data (ukpds)

When they compared the life expectancy of the SU/Insulin group with the conventional group, the SU/Insulin group gained 1.1 (0.3-2.0) years. The SU/Insulin group also gained 0.9 (0.2 – 1.5) QALYs compared with the conventional group. Participants on metformin gained 2.7 (1.0 – 4.4) years of life and 2.0 (0.7 – 13.2) QALYs compared to the conventional group.

Figure 5: Quality Adjusted Life Years in UKPDS 44 years Follow-Up and Cost effectiveness

New results: from 44 year follow-up

Quality Adjusted Life Years:
Metformin vs. Conventional Glucose Control

QALYs*
Metformin: 17.5 QALYs
Conventional: 15.6 QALYs
Difference: 2.0 (0.7, 13.2) QALYs
(95% CI)

— Metformin — Conventional ☐ Difference in life expectancy

*Adjusted for censoring

(ukpds)

Dementia

Patients with diabetes have a 60% higher risk of all forms of dementia [3]. Most glucose lowering agents except insulin reduce the risks although the results are conflicting because most of the studies are too small or too short. There are only a few ongoing trials looking at effect of glucose lowering agents on dementia.

In the 44-year follow up of the UKPDS, the effect of 10 years of treatment with SU/Insulin range from 4% increase to a 29% reduction when compared with conventional treatment. The effect of 10 years of treatment with metformin range from an 18% increase to a 49% reduction when compared with conventional treatment. The effects were not statistically significant. The authors did acknowledge that they did not have primary care data and dementia was not always recorded.

Figure 6: Relative Risk Reduction of Complications
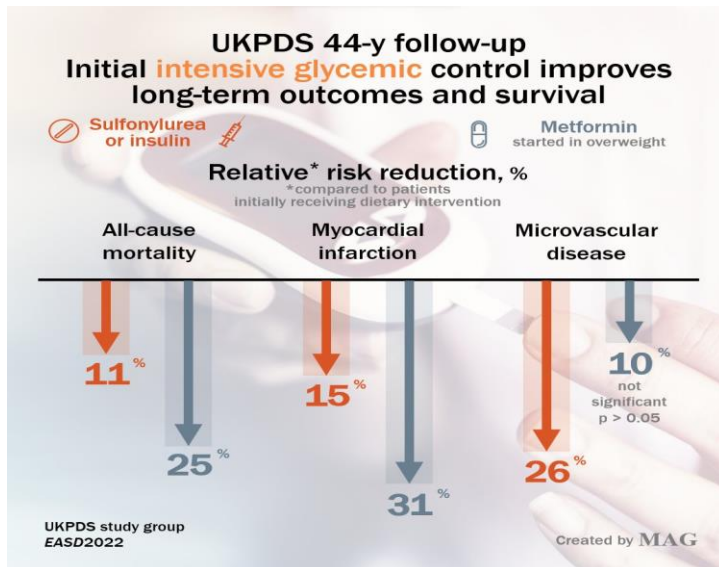
In summary, the legacy effect of early glycaemic control first identified in the UKPDS 30-year analyses remain essentially unchanged up to 44 years of follow-up. Early intensive treatment with SU/Insulin led to a **11% reduction in deaths** and **26% reduction in microvascular complications**. The metformin intensive treatment started from beginning led to a **25% overall reduction in all cause-deaths** and **31% reduction in myocardial infarction**. These landmark findings emphasise the importance of diagnosing diabetes early and treating intensively from day 1[4].

It is thought that suboptimal glycaemic control induces permanent pathophysiological alteration which increases the risk of diabetic complications and premature mortality. Metformin, in addition to reducing hyperglycaemia, has additional legacy effect suggesting that metformin may have other protective mechanisms.

References:

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Not applicable

- Conflict of Interest Statement

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