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| Institution: The University of Oxford |
| Unit of Assessment: 1 |
| <p>Title of case study:</p> <p style="text-align: center;">DEFINING TYPE 2 DIABETES IN THE UNITED KINGDOM</p> |
| <p>Summary of the impact:</p> <p>The University of Oxford's United Kingdom Prospective Diabetes Study (UKPDS) was a landmark 30-year clinical trial, reported in over 80 academic research papers between 1983 and 2008. It showed beyond doubt that diabetic complications, previously thought to be inevitable consequences of the condition, could be delayed or prevented by improved treatment from the time of diagnosis. These findings have had a profound influence on the management of type 2 diabetes, clinical guidelines, and standards of care, and have reduced diabetes-related complications worldwide, lowering the incidence of blindness, kidney failure, amputation, heart attack and stroke.</p> |
| <p>Underpinning research:</p> <p>In 2011 2.9 million people within the UK and 346 million people worldwide were known to have diabetes. With these numbers increasing every year, the World Health Organization has projected that deaths from diabetes will double between 2005 and 2030. More than 90% of patients diagnosed with the disease suffer from type 2 diabetes. Predominately the result of obesity and physical inactivity, clinicians had long suspected an association between the complications of type 2 diabetes and elevated blood glucose levels, without quantifiable proof.</p> <p>The UK Prospective Diabetes Study (UKPDS) was a 20-year prospective randomised controlled clinical trial of 5,102 newly diagnosed type 2 diabetic patients from 23 clinical centres across the UK, which concluded in 1997. The trial was designed to determine whether improved blood glucose and improved blood pressure control in hypertensive patients could prevent complications and reduce the incidence of mortality. Conceived and initiated by the late Professor Robert Turner and Professor Rury Holman at the University of Oxford's Diabetes Trials Unit, the UKPDS was the largest clinical research study into diabetes ever conducted at the time of publication.</p> <p>Results of the trial showed that:</p> <ul style="list-style-type: none"> • intensive glucose control following the diagnosis of type 2 diabetes improved patient health in the long-term¹; • tight blood pressure control following the diagnosis of type 2 diabetes improved patient health in the long-term² ; • treating patients with metformin reduced cardiovascular disease outcomes, with a 36% relative risk reduction in mortality and a 39% relative risk reduction in myocardial infarction³; • demonstrated for the first time that type 2 diabetes is a progressive condition requiring multiple therapies over time⁴; • using metformin to treat overweight patients with type 2 diabetes was cost effective⁵. <p>But the findings of the Oxford-run UKPDS did not end in 1998. Following completion of the trial all patients returned to their usual healthcare providers but continued to be monitored for diabetic complications for an additional ten years. The results of the UKPDS post-trial monitoring study,</p> |

Impact case study (REF3b)

published in 2008, showed that intensive glucose control beginning as soon as type 2 diabetes was diagnosed, led to a 'legacy effect' of sustained and extended benefits in the longer term, with a 15% reduced risk of heart attacks and 13% fewer deaths in patients⁶.

This post-trial monitoring study also showed that the benefits of earlier improved blood glucose, as well as the earlier use of metformin, in overweight patients continued to provide benefit for ten years after the trial was completed⁶. With 83 primary papers published, and well over 10,000 citations, the UKPDS has influenced clinical understanding of diabetes and improved its management worldwide.

References to the research:

1. UK Prospective Diabetes Study (UKPDS) Group Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*. **352**:837-53; (1998) **UKPDS paper showing how intensive glucose control following the diagnosis of type 2 diabetes improved long-term patient health.**
2. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Brit Med J.*; **317**:703-13.(1998) **UKPDS paper showing how tight blood pressure control following the diagnosis of type 2 diabetes improved long-term patient health.**
3. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet*. **352**, 854-65(1998). **UKPDS paper showing how metformin treatment reduced cardiovascular disease outcomes.**
4. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA*. 1999;**281**, 2005-12(1999). **UKPDS paper showing that type 2 diabetes is a progressive condition requiring multiple therapies.**
5. Clarke P et al Cost-effectiveness analysis of intensive blood glucose control with metformin in overweight patients with type 2 diabetes. UKPDS No. 51 *Diabetologia*. **44**, 298-304(2001). **Paper showing that treating overweight patients with type 2 diabetes with metformin was cost effective.**
6. Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R. & Neil, H. A. W. 10-year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.* **359**, 1577–1589 (2008). doi: 10.1056/NEJMoa0806470 **Paper describing the legacy effect identified by the 10-year UKPDS post trial follow-up study.**

The UKPDS received funding from the UK Medical Research Council, the British Diabetic Association, the UK Department of Health, the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Disease (the US National Institutes of Health), the British Heart Foundation, The Wellcome Trust, the Charles Wolfson Charitable Trust, the Clothworkers' Foundation, the Health Promotion Research Trust, the Alan and Babette Sainsbury Trust, the Oxford University Medical Research Fund Committee.

Details of the impact:

The UKPDS publications are landmark studies in the treatment of type 2 diabetes. They have influenced diabetes treatment guidelines and standards of care worldwide^{7,8}, leading to earlier and more effective therapy globally for people with diabetes.

Impacting clinical guidelines

References to UKPDS publications can be found in virtually all evidence-based international guidelines⁹, including the UK National Institute for Clinical Excellence Guidelines¹⁰, International Diabetes Federation Global Guidelines⁸, British Columbia Guidelines¹¹, and the Australian National Health and Medical Research Council Guidelines for Blood Glucose Control in Type 2 Diabetes¹². Each of these guidelines reflect UKPDS findings by recommending intensive glucose control and tight blood pressure control following the diagnosis of type 2 diabetes, as well as the use of metformin as the first-line treatment for type 2 diabetes. In addition, the first joint consensus guidelines from the American Diabetes Association and European Association for the Study of Diabetes explicitly state that metformin should be the foundation therapy, along with diet, in patients with type 2 diabetes¹³. These guidelines were also based on evidence presented in the UKPDS. As a result, metformin is now the most commonly prescribed therapy for diabetes worldwide^{14,15}.

Educating the medical community and the public

The UKPDS trial quickly became a staple in many of the tens of thousands of continuing medical education programmes on type 2 diabetes and its management since 1998. The findings have been cited in educational material aimed at healthcare professionals including nurses and dietitians, and formed part of the information given to the public⁷.

Impact on patients

The complete impact of this study is impossible to quantify, however a number of experts have given their opinion on the very large impact the UKPDS trial has had on patients and the lives of those living with diabetes. For example, writing in the recently published 'Understanding Medical Research, the Studies that Shaped Medicine', Philip Home comments that the UKPDS trial affects the lives of over 200 million people every day¹⁶. And in his paper *in Diabetic Medicine* Genuth writes that the UKPDS has contributed to the slow overall global trend of decreasing HbA_{1c} levels – a measure of the average amount of sugar in the blood - of treated diabetic patients⁷.

Given its influence on the development of guidelines, clinical education and the thinking of healthcare professionals, Philip Home, this time writing in *Diabetic Medicine*, concludes that “by inference it must be responsible for a significant part of the improvement in health outcomes in people with type 2 diabetes in the last decade”⁹. It is likely that the impact of UKPDS is not yet fully realised. Data from the uniquely valuable cohort of patients in this study are likely to yield even more insights into diabetes, complications and benefits of treatment in the years to come⁷.

Sources to corroborate the impact:

7. Genuth, S. The UKPDS and its global impact. *Diabet. Med.* **25 Suppl 2**, 57–62 (2008). doi:10.1111/j.1464-5491.2008.0204.x. **Paper summarising global impact of UKPDS.**
8. International Diabetes Federation Clinical guidelines task force Global Guideline for Type 2 Diabetes Chapter 9. Glucose control:oral therapy [online] (2005). Available at: <http://www.idf.org/webdata/docs/GGT2D%2009%20Oral%20therapy.pdf> [Accessed 2013] **The International Diabetes Federation's guidelines for treating diabetes with oral therapy.**
9. Home, P. D. Impact of the UKPDS--an overview. *Diabet. Med.* **25 Suppl 2**, 2–8 (2008). doi:10.1111/j.1464-5491.2008.02501.x. **Paper summarising impact of the UKPDS trial.**
10. National Institute for Health and Clinical Excellence (NICE) Guidelines, UK. Type 2 diabetes: The management of type 2 diabetes. [online] March 2009 Available at: <http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf> [Accessed 21st June 2013] **Clinical guidelines outlining recommendations for management of type 2**

diabetes in the NHS in England and Wales.

11. British Columbia Ministry of Health Guidelines. Diabetes Care. [online] September 2010. Available at: http://www.bcguidelines.ca/guideline_diabetes.html [Accessed 21st June 2013] **Clinical guidelines outlining recommendations for diabetes care in British Columbia.**
12. Australian Government National Health and Medical Research Council. National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes [online] July 2009. Available at: <http://www.nhmrc.gov.au/files/nhmrc/publications/attachments/di19-diabetes-blood-glucose-control.pdf> [Accessed 21st June 2013] **Clinical guidelines outlining type 2 diabetes blood glucose control recommendations in Australia.**
13. Nathan DM, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. **52**:17-30. 2009 doi: 10.1007/s00125-008-1157-y **First joint consensus guidelines for glucose control in type 2 diabetes from the American Diabetes Association and European Association for the Study of Diabetes.**
14. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update).[online] London: Royal College of Physicians, 2008. Available at: <http://www.nice.org.uk/nicemedia/pdf/CG66FullGuideline0509.pdf>. [Accessed 21st June 2013] **UK clinical guideline for type 2 diabetes management.**
15. American Diabetes Association Standards of medical care in diabetes--2009. *Diabetes Care*, **32 Suppl 1**, S13–61. (2009). doi:10.2337/dc09-S013 **References to the UKPDS can be found in this article about the standards of medical care in diabetes.**
16. Home, P Diabetes Therapy and the Prevention of Vascular Damage In Goodfellow, JA, ed. *Understanding Medical Research: The Studies that Shaped Medicine*, 1st ed. Chichester. Wiley-Blackwell.2012. pp.235-245. **Commentary summarising the vast effect of the UKPDS trial on the lives of patients.**