Challenges in the management of younger adults with Type 1 Diabetes in hospital Outpatient and Inpatient settings.

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine by

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2. Dedication

To Hils, Ben and Ellie,

Thank you for your patience and understanding, without that, this thesis would never have been finished.
3. Abbreviations
Detailed below are the commonest abbreviations used in this thesis.

T1DM- Type 1 Diabetes
T2DM- Type 2 Diabetes
DCCT- Diabetes Control and Complications Trial
EDIC- Epidemiology of Diabetes Interventions and Complications
NICE- National Institute of Clinical Excellence
NSF- National Service Framework
SHA- Strategic Health Authority
QoF- Quality Outcomes Framework
GMS- General Medical Services
GP- General Practitioner
GPwSI – GP with a special interest
IHD- Ischaemic Heart Disease
CVD- Cerebro-vascular Disease
PVD- Peripheral Vascular Disease
BP- Blood pressure
HbA1c- Haemoglobin A1 concentration (DCCT aligned)
IVDU- Intravenous drug User
DM- Diabetes mellitus
PCT- Primary Care Trust
ADA – American Diabetes Association
NHS – National Health Service
4. Aims
The delivery of diabetes care has changed significantly over the last 30 years; virtually all aspects of treatment have altered or progressed. The routine measurement of biochemical markers are being used to gauge this progress.

This thesis aims to examine some of these changes on a “real-world” group of patients with type 1 diabetes (T1DM). Such changes have occurred and are derived from an evidence base of clinical trials in specially selected groups of volunteer patients. Although this can demonstrate the effect of these interventions, there always remains the question of whether the findings can be translated into practice with ‘real-world’ patients.

The effects of such interventions, particularly those in diabetes care, may take years to be apparent. It is therefore difficult to study such things in a prospective way within the context of an MD thesis. Using a retrospective analysis of a large patient cohort, with T1DM, who have been attending the same diabetes clinic since its inception, it has been possible to examine some of the outcomes of these patients in view of the changes that have occurred in diabetes practice over the last 10 -15 years.

- Firstly a comparison is made between the patient cohort from the clinic and the trial population of the landmark diabetes study; the DCCT¹. The study examines if the goals of the DCCT are achievable in a “real-world” group of patients, the results of which are given in chapter 8.
- Tight glycaemic control has become central to diabetes care post-DCCT. Further interventional studies, albeit predominantly in patients with T2DM, have demonstrated the benefits of aggressive management of risk factors for cardiovascular disease in patients with diabetes. Subsequently aggressive management of hypertension and dyslipidaemia has become the standard practice in guidelines for the management of T1DM. The clinic cohort studied
in this thesis has lived through these changes and it has been possible to assess if the implementation of these guidelines, for the management of lipids, blood pressure and glycaemic control, has made any measurable difference; this is described in chapter 9.

- Most T1DM care is delivered in an outpatient setting. However some patients with T1DM do require care as hospital inpatients. A comparison of the one day prevalence of diabetes patients in hospital in 1991 and 2003 is discussed in chapter 10. This is particularly relevant given the increasing interest in diabetes inpatients².

- In our hospital practice we noted a further group of patient with T1DM that were frequent hospital inpatients. These patients, all of whom had problems associated with intravenous drug abuse, were followed-up and their outcomes reported in chapter 11. These patients pose significant problems and challenges for the inpatient diabetes team.

This thesis therefore aims to examine how successful the implementation of major trial evidence and guideline is at achieving results in the “real-world” and reviews what factors may limit success. Outpatient diabetes care provides the majority of the work for patients with diabetes. However, inpatient diabetes care remains a significant issue. Diabetes patients frequently spend longer in hospital than patients without diabetes and this is examined and discussed.
5. Introduction
Diabetes mellitus is a common chronic disease with an increasing incidence and prevalence. Predominantly, this has occurred in type 2 diabetes (T2DM) a problem which is associated with increasingly sedentary lifestyles, weight gain and decreased regular exercise. There have also been increases in the incidence and prevalence of type 1 diabetes (T1DM). Recent estimates have suggested an annual increase in incidence of ~3% per year in Europe and a potential doubling of new cases in children under 5 years old within the next 20 years. Patients with T1DM and T2DM can develop complications which in the long term result in increased morbidity and mortality and considerable resources from the healthcare systems caring for them.

Microvascular disease in T1DM and T2DM, in the form of diabetic retinopathy, nephropathy and neuropathy may lead respectively to visual impairment and blindness, end-stage renal failure, dialysis and lower limb amputation as a result of ulceration and chronic infection. These issues have a significant impact on the patient and the healthcare-systems supporting them. Macrovascular disease, (Ischaemic heart disease (IHD), cerebro-vascular disease (CVD) and peripheral vascular disease (PVD)), occurs with greater prevalence in patients with T1DM and T2DM than in the non-diabetic population. Increasing numbers of patients with T1DM are surviving into old age and macrovascular disease is seen more frequently and consequently requires more support and management. This thesis will discuss some aspects of these issues with relevance to patients who have T1DM.

The management of any disease can vary depending on its setting and it is important to outline the many factors which have resulted in the system of care we now deliver to patients with T1DM. This introduction will summarise how the recognition and treatment of hyperglycaemia improves the morbidity and mortality and how healthcare systems have adapted to delivering this care.
5.1 Historical Perspective

The introduction of insulin injections into diabetes practice took place in 1923. It was discovered in Toronto during 1921-22 and the Nobel Prize was awarded to Frederick Banting and J.J.R. Macleod in 1923. There remains controversy over this award as both Banting and Macleod each immediately called for the recognition of the people they also felt should have been acknowledged. In Banting’s case this was Charles Best, a young science student, with whom he did the experimental work. While Professor Macleod announced he would share the award with J.B. Collip, a biochemist that joined the research in late 1921. The details of the discovery of insulin is a book in itself and it is more commonly accepted that the experimental work leading to the identification and isolation of insulin was done by Banting and Best.

Diabetes has been recognised for thousands of years. The characterisation of the disease may usefully be described in periods; The Ancient period, The Diagnostic period and The Experimental period.

The Ancient period: from ~1550 BC onwards.

Ancient documents such as the Ebers papyrus, found in Thebes in 1862, documented many disease states, amongst which one that resembled diabetes was noticeable. Diabetes, as a term to describe a condition, was first used by Areteaus of Cappadocia in ~2nd century AD. It is a term from Ionian Greek and means ‘to run through’.

The urine in patients with diabetes was noted to taste sweet as early as the 5th and 6th century AD and was documented in Arabic texts in the 9th-11th centuries, particularly those of Avicenna, who describes such complications as gangrene and collapse of sexual function.
The Diagnostic Period - 16th Century onwards.

In the 17th century, English physician Thomas Willis made reference to the sweetness of diabetic urine. Around this time Thomas Sydenham speculated that diabetes was a systemic disease arising in the blood, where 'chyle' was incompletely absorbed. In the 1776 a Liverpool physician named Matthew Dobson published his account of a series of experiments and observations on the urine and blood of one of his typical patients with diabetes, Peter Dickonson. This paper was groundbreaking; confirming that urine was sweet to taste but also the serum taken from the patients’ blood tasted sweet, thus discovering hyperglycaemia. Such an observation helped divert diabetes research towards a study of how the body deals with carbohydrate foods.

The Experimental Period – 19th Century onwards.

During this period, Claude Bernard (left) and Paul Langerhans (below) demonstrated how the liver stored glucose as glycogen, and how the pancreas contained cells that did not appear to be concerned with its’ digestive secretions. In 1889 Oskar Minkowski and colleagues performed a pancreatectomy on a dog to determine if digestion of fats could still occur. As an unintended side-effect they rendered the dog diabetic. This was confirmed on repeated study. Further experiments with ligated pancreatic ducts showed that the digestive secretion was not responsible for
blood sugar control. An *internal* secretion of the pancreas had this role. Around 1900 Georg Ludwig Zuelzer discovered that pancreas extract reduced the sugar excreted in the urine of two diabetic dogs. Encouraged by this discovery, in 1906 he twice injected a dying diabetic man with pancreas extract, and although no sugar measurements were made, the patient came out of the coma and his appetite returned. Unfortunately there was no more pancreas extract to use and the patient subsequently died. By 1913 many people were interested in diabetes research. Indeed J.J.R Macleod a noted physiologist published *Diabetes: Its Pathological Physiology*. He concluded that there was an internal secretion of the pancreas, but suggested several reasons why it might never be captured in pancreatic extract. Researchers continued to work on pancreatic extract, including Israel Kleiner a young American working at the Rockefeller Institute and Nicholas Paulesco, professor of physiology at the Romanian School of Medicine, both had their work interrupted by the war, his findings in 1920 and also demonstrated a fall in blood sugar after injection of pancreas extract into dogs. Whilst this work continued, Frederick Banting had qualified as a surgeon from the University of Toronto in 1917. He was also involved in the Great War, not returning home until 1919 He opened a doctors’ office in 1920. During late October 1920 he prepared a talk on carbohydrate metabolism and read an article entitled: “The relation of the Islets of Langerhans to Diabetes with special reference to cases of pancreatic lithiasis” by Moses Barron. It struck Banting that the pancreatic degeneration that occurred during chronic lithiasis could be created by Paulesco.
had to halt his research in 1916, until resumption in 1919. He published his findings in 1920 and also demonstrated a fall in blood sugar after injection of pancreas extract into dogs. Whilst this work continued, Frederick Banting had qualified as a surgeon from the University of Toronto in 1917. Pancreatic duct ligation. The remaining islets could then be studied to see if the internal secretion could be obtained and identified. He subsequently approached Professor James Macleod at Toronto University in an attempt to start researching this theory. Initially sceptical, Macleod relented and suggested he try over the summer period with some help from the physiology student Charles Best (seen left, with F Banting and experimental dog). They commenced work in May 1921. During the summer of 1921 and into 1922 they continued their work, joined later by James Collip a PhD biochemist. By December 30 1921, they presented a paper to prominent people in diabetes research at the American Physiological Society Conference. The paper was entitled: ‘The Beneficial Influences of Certain Pancreatic Extracts on Pancreatic Diabetes. The meeting was not a great success as many flaws in the research were identified. This somewhat served to focus the groups’ direction. By improving extraction techniques and purification methods they were ready to try the extract on humans, and on 23rd January 1922, a young man with diabetes, Leonard Thompson received the first injection of this purified extract given to a human. A hypoglycaemic response was found and continued on further administration. By May 3rd 1922 the group announced that they had isolated the internal secretion of the pancreas and they called it insulin.
Although a ground-breaking announcement, months of difficulties followed particularly concerned with the problems of large scale isolation and production. Eli Lilly Company stepped in to help, and after some difficulties initially, the production of insulin in reasonable quantities began in August 1922. Initially beef insulin was isolated from the pancreases of cows and provided a decent volume of insulin extract.

The purity of this extract remained an issue and reactions to injections of it remained a problem until purification techniques improved. Pig insulin was also produced and used as an alternative to bovine insulin and but as before purity issues and reactions to injections were also noted.

In 1936, as the purity of both extract increased, insulin was combined with protamine- a protein from river trout semen- to delay absorption and produce slow-release insulin. The further addition of zinc led to the production of the first long acting insulin, Protamine-Zinc insulin (PZI). In 1950 the production and sale of a long acting insulin named Neutral Protamine Hagedorn (NPH) began. It had the advantage of being able to form crystals and the ability to be mixed with shorter acting insulin to form a combination treatment.
Eventually technology and research facilitated the development of human insulin. Research during 1963-66 in Germany, China and the United States demonstrated human insulin could be synthesised and in 1975 fully synthetic insulin (CGP 12831) was produced by Ciba-Geigy laboratories in Basel, Switzerland. Subsequently, human analogue insulin was developed by genetic manipulation in 1980 and was first tested on 17 volunteers in England. This form now dominates insulin use in current clinical practice\textsuperscript{20-22}. During this development the way insulin was delivered and various factors affecting the way it was absorbed also influenced current practice and this is discussed later.
5.2 Hyperglycaemia and Outcomes.

5.2.1 Microvascular Disease in T1DM

By the 1950s patients treated with insulin were noted to develop complications, particularly those affecting the kidneys and eyes. Early observational studies in the 1950s and 1960s associated the prevalence of these complications with the presence of high blood or urinary sugar. The ability to control glucose variations improved with the development of shorter and long acting insulin, but also with the improved method of measuring blood glucose when compared to urinary glucose measurement.

In the late 1970s and early 1980s a number of early interventional studies examined how attempting to control the blood sugar over and above the goal of removing osmotic symptoms would affect the development or progression of microvascular disease. Studies such as the STENO I and STENO II studies demonstrated the benefit of good blood glucose control in the development of microvascular complications.

It took the Diabetes Control and Complications Trial (DCCT) interventional study to definitively demonstrate the benefits of good glucose control in a population of patients with T1DM compared to a group of patients who received, what was then termed ‘standard-care’. Subsequent to the publication of the DCCT the ‘standard’ management of patients with T1DM shifted more towards tighter blood glucose control with the aim of reducing microvascular complications.
5.2.2 Macrovascular Disease in T1DM.

Patients with T1DM also suffer significant macrovascular disease. This had been recognised as a complication associated with T2DM for many years. Hyperglycaemia was thought to be a contributing factor but even well controlled patients with T1DM had an excess of macrovascular disease compared to the non-diabetic population.

Traditional risk factors for IHD, CVD and PVD, such as smoking, hypertension and hyperlipidaemia have all been studied in patients with T1DM and the effects over and above good glucose control noted. The management of patients with diabetes has more recently moved towards addressing these risk factors as well as controlling blood glucose. The evidence for intervening in patients with T1DM who have elevated blood pressure and cholesterol is variable. There is strong evidence that links poor diabetes control with diabetic nephropathy and patients with nephropathy have also been shown to hypertension more frequently than those without nephropathy. Whether the existence of hypertension predates the development of nephropathy is unclear, but the observation of their co-existence is associated with an increased risk of death from macrovascular disease (IHD/CVD) and progression to end-stage renal failure. Consequently, newer consensus guidelines have included the aggressive management of hypertension in patients with evidence of diabetic nephropathy27-29.

The evidence for managing dyslipidaemia in patients with T1DM is not clear cut. In patients with T2DM there is good evidence for the existence of a specific dyslipidaemia associated with an elevated low-density lipoprotein cholesterol (LDL-C) which is small, dense and athrogenic. Treatment with lipid lowering drugs in these patients is undoubtedly beneficial30, improving cardiovascular risk and overall mortality. In patients with T1DM this dyslipidaemia is less frequently found. Often a
normal a near normal profile predominates or hypertriglycerideamia is seen. Improvement of glycaemic control often corrects this\textsuperscript{31}.

The cardiovascular benefits of lowering lipids in T2DM, has however, led to a trend towards aggressive lipid management in patients with T1DM. There is evidence of benefit in addressing cardiovascular risk factors in patients with T1DM and nephropathy\textsuperscript{32}. However the benefit of cholesterol management in patients with T1DM but without nephropathy is less clear\textsuperscript{33}. The most recent guidelines recommend lipid-lowering therapy only in those patients with persistent poor control, long duration of diabetes or the co-existence of other risk factors\textsuperscript{34}.

More recent evidence has shown that intensive diabetes control – as used in the DCCT trial – has long term beneficial effects on surrogate markers of\textsuperscript{35}, as well as on the actual risk of cardiovascular disease in patients with T1DM\textsuperscript{36}. These effects appear as the duration of diabetes increases, although there appears to be an independent association with the degree of glycaemia\textsuperscript{11}. These issues are discussed further in the literature review.
5.3 Technologies, Insulin and drugs.

5.3.1 Delivery Technologies

The improvements in diabetes care have often been mirrored by improvements in the medications such as the development of human then analogue insulins and technologies used to manage diabetes.

Insulin Injection devices

Initially insulin was administered via a glass syringe and a standard metal needle. The first commercially available glass syringe was made by Becton, Dickinson and Company in 1924. Insulin injection was time-consuming and had numerous problems associated with it such as repeated use and sterilisation of insulin injection equipment and needles. By 1952 the first sterile disposable syringes were available. Accompanying this was the development of smaller, thinner and consequently less painful needles for injection. By 1969 the first disposable self-contained syringe and needle was available. The development in 1985 of the first ‘pen-device’ and pen needle for administering insulin was a major step forward. The Novopen was launched by Novo Nordisk but was quickly followed by pen devices made by other manufacturers. Pens have quickly established themselves as a popular method of insulin delivery where they are available, they are clearly convenient and patients report satisfaction and improved quality of life with their use.

Insulin pump devices

The development of the continuous subcutaneous insulin pump has also provided patients with an alternative source of insulin delivery. Initially, when pumps were developed in the 1960s, they were cumbersome and prone to failure. Over the years the technology progressed to with pumps becoming increasingly miniaturised. Current models are hardly bigger than a credit-card (Fig 5.3.1).
In selected T1DM patient groups improvements in quality of life are documented\(^{41}\). It is clear however, that pump technology is not suitable for use by all patients\(^{42-44}\). These pumps are external devices; however implantable pump devices were also developed. Whilst external pumps use the subcutaneous delivery method, implantable pumps deliver insulin into the peritoneal cavity, which offer the promise of a more physiological insulin delivery, it being absorbed directly into the portal system. The initial implantable pumps were designed and made in the 1970s, for example the Infusaid pump\(^{45}\); more sophisticated pumps following in the 1980s. However by the 1990s only one pump was being manufactured – the MiniMed Implantable Pump\(^{46}\). The necessity of having to undergo a surgical procedure for implantation was always an issue with these pumps, as well as other associated problems of use. They have not made the transition into routine clinical use but are still used in research settings or part of specially selected centres.
Alternate delivery devices and routes

Further alternative insulin delivery methods have also been developed. An inhaled insulin device was launched in September 2006 but its uptake and use by clinicians was low and the reasons for this have been discussed in the literature\textsuperscript{47-49} major influences were the lack of long-term safety data, the unknown long-term effects of insulin on lung function and the cautious nature of many practicing clinicians. The National Institute of Clinical Excellence (NICE) also advised limitations on its’ use\textsuperscript{50} and in April 2007 it was subsequently withdrawn from sale in the UK, although support exists for those still using it. The use of inhaled insulin may reappear at a later date as the licence for the technology used to create and deliver this form of insulin has been taken over by another company. Other methods of insulin delivery such as buccal\textsuperscript{51}, intranasal\textsuperscript{52} and oral insulin\textsuperscript{53} have also been examined, however their success at providing insulin at doses to be effective in clinical practice has been poor.

5.3.2 Monitoring Technologies

Urine testing

Methods to detect glucose in urine preceded the use of insulin by many years. For example, Francis Home detected glucose in urine by fermentation demonstration in 1780\textsuperscript{54}. Once blood glucose concentration exceeds the renal threshold for disposal of glucose, approximately 11 mmol/l, then it appears in the urine and is detectable. As with other investigations, urine testing has subsequently developed into sophisticated multi-test urinalysis which allows detection of glucose, ketones and other products in the urine. Initial testing was much more problematic though, Benedict's solution was in common use in the 1930s and 1940s and required the tester to boil the reagents for five minutes to detect glycosuria\textsuperscript{55,56}. These issues
were resolved as technology developed, Bayer Laboratories producing effervescent tablets (Clinitest, 1941) which simplified this reaction to a more practical user-friendly test. Subsequently dip and read clinical test strips (Clinistix, 1956) were developed for the detection of glucose in urine. This test used the process of enzymatic breakdown of sugar followed by an oxidation reaction. The oxidation causes a colour change which is proportional to the sugar content of the urine. This colour is then compared to a visual read strip. The convenience of these tests led to their widespread use. By the 1960s Bayer had developed a test strip for detecting and quantifying the amount of glucose in blood (Dextrostix) using the same method described above.

The measurement of proteins in the urine, initially albumin and subsequently microalbumin followed a similar course of development. Originally albumin in the urine was detected by heating and observation. Richard Bright commented on “albuminous nature of urine” in his description of the clinical symptoms of nephritis in 1827 in “Reports of Medical Cases”. In the following years test strips were developed to detect protein in the urine. Subsequently clinical studies demonstrated it was a good predictor of worsening renal disease. However tests which identified the presence of protein in the urine in ‘micro’ amounts, allowed earlier intervention to occur. The subsequent tests for ‘micro’-albuminuria followed: radial immunodiffusion, immunoelectrophoresis, radioimmunoassay, enzyme immunoassay, latex-bead immunoagglutination, turbidimetric immunoassay and dye-binding. Such testing is now a part of routine diabetes care, aiding in the early identification and management of previously undetectable renal disease.

**Blood testing**

Urinalysis for glucose control has been superseded by accurate methods of assessing capillary blood glucose concentrations. This has become a very useful
method of guiding insulin doses and monitoring glucose excursions. Capillary blood ketone testing has also demonstrated its value in clinical use\textsuperscript{60, 61}.

Bayer once again led the way, after developing Dextrostix, they introduced the first portable blood glucose meter- known as the Ames Reflectance Meter (ARM, Fig 5.3.2.1).

![Ames Reflectance Meter, 1969.](image)

Dextrostix were a visual test strip, meaning that after exposure to blood the strip would change colour, by a chemical reaction in response to the blood glucose, and this would be visually compared to a chart giving a glucose concentration. This method was semi-quantitative and as such, prone to error. The reflectance meter replaced the visual comparison and read the strips directly, the needle deflecting along the scale to give a glucose concentration. Although this improved accuracy of readings they were still error prone. Subsequent modifications of the ARM by Bayer improved its function and accuracy and by the 1980s they were producing the Glucometer and Dextrometer. These were then quickly followed by meters produced by other companies, such as the Accu-Check meter by Boehringer-Mannheim-
which used Chemistrip bG and the Medisense meter by Abbott. The Chemistrip bG developed into the most frequently strip used and became known as the BM stick after the company which made it. The Medisense meter was a technological breakthrough as it was the first electro-chemical based meter and therefore did not rely on light reflectance of a colour change to be interpreted by the meter. This improved the accuracy of the readings and as a consequence their reliability and clinical usefulness\textsuperscript{62, 63}.

Once it became clear that good glycaemic control was associated with long term microvascular outcomes such as retinopathy and nephropathy then home blood glucose monitoring became important, and soon moved from a tool used to assess glucose variations into an intrinsic part of diabetes management, particularly in intensive regimes\textsuperscript{64-66}.

**Continuous glucose monitoring systems (CGMS)**

The development of the continuous glucose monitoring system (CGMS) in the late 1990s\textsuperscript{67, 68} allowed the study of glucose variability, via 288 separate measurements over a 72 hour window. Initially used in paediatric practice, the CGMS is increasingly being used in other patients with type 1 diabetes to help improve control. It is particularly useful at helping identify periods of unrecognised hypoglycaemia\textsuperscript{69}, notably overnight, but also in tailoring intensive insulin regimes so that wide glucose variability is avoided. Such systems are one of the many tools used to optimise control for patients with T1DM, although the evidence for improvement in glycaemic control is still variable\textsuperscript{70-72}, it does help patients gain a greater understanding of the relationship between glucose excursions and insulin use.

**Glycated Haemoglobin**

The analysis of blood proteins, including haemoglobin and the effect of glucose upon them has also been studied. This led to the development of the fructosamine\textsuperscript{73}. 


and haemoglobin A1 tests\textsuperscript{75, 76}. The latter test was modified and standardised to the currently used HbA1c (DCCT aligned). This has shown significant correlation with long term complications and has become one of the standard tools by which insulin therapy is guided\textsuperscript{77}.

Further standardisation of the HbA1c assay is currently taking place, this will allow international comparisons to be more accurate\textsuperscript{77}, that and rigorous comparisons between international area maintain these standards\textsuperscript{78}.

More recently debate has been ongoing within the diabetes profession about the use of HbA1c as a monitoring tool in comparison with the a measure known as estimated average glucose (eAG)\textsuperscript{79-81}. Both measures have their uses, eAG being a more patient centred measure as it relates to self-monitored glucose values. However, HbA1c has been definitively shown to correlate with microvascular disease and thereafter complications, and so provides a useful tool for management. The most popular measure will prevail in due course, although it would be reasonable to expect both will be used in clinical practice.

Such technological advancements have made the monitoring of diabetes easier and have allowed improvements in glucose control to occur. This has coincided with improved insulins which have enabled more flexibility and adaptability in their use compared to previous types of insulin.
5.3.3 Insulin Technology

The introduction of insulin into the treatment of T1DM was a medical milestone, since that time however it has become apparent that insulin replacement would be more effective if it mirrored the normal physiological production of insulin.

Physiological insulin release in non-diabetic healthy people is a dynamic response between the metabolic requirements for fuel and glucose production. In basic terms a 'basal' level of insulin is secreted in pulses; with a secondary surge in insulin production on consumption of a meal. This response ensures adequate disposal of new glucose into active metabolic processes e.g. exercise or into storage. Mirroring this physiological pattern by injecting deposits of insulin subcutaneously is difficult. As technology has progressed attempts have been made to develop insulin which would approximate the physiological response.

Insulins can usefully be divided into the following categories on their putative duration of action:

- **Rapid-acting:** Insulin lispro, Insulin aspart, and Insulin glulisine
- **Short-acting:** Regular (soluble) Insulin
- **Intermediate-acting:** NPH (isophane) Insulin
- **Long-acting:** Insulin glargine and Insulin detemir

A table of their onset, peak and duration of action is given (table 5.3.3.1).
Table 5.3.3.1 – Time profiles of human and analogue insulin.

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Onset of Action (h)</th>
<th>Peak action (h)</th>
<th>Effective duration of action (h)</th>
<th>Maximum duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro (Humalog)</td>
<td>¼ - ½</td>
<td>½- 1 ¼</td>
<td>3-4</td>
<td>4-6</td>
</tr>
<tr>
<td>Insulin aspart (NovoLog)</td>
<td>¼ - ½</td>
<td>½ -1 ¼</td>
<td>3-4</td>
<td>4-6</td>
</tr>
<tr>
<td>Insulin glulisine (Apidra)</td>
<td>¼ - ½</td>
<td>½ -1 ¼</td>
<td>3-4</td>
<td>4-6</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (soluble)</td>
<td>½ - 1</td>
<td>2-3</td>
<td>3-6</td>
<td>6-8</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (isophane)</td>
<td>2-4</td>
<td>6-10</td>
<td>10-16</td>
<td>14-18</td>
</tr>
<tr>
<td><strong>Long-acting analogue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine (Lantus)</td>
<td>3-4</td>
<td>8-16</td>
<td>18-20</td>
<td>20-24</td>
</tr>
<tr>
<td>Insulin detemir (Levemir)</td>
<td>3-4</td>
<td>6-8</td>
<td>14</td>
<td>~20</td>
</tr>
</tbody>
</table>

This is sometimes displayed as a time-action profile, as seen below (as an idealized version). This demonstrates the difference between insulins and the duration of time over which they are effective.

Insulins have developed considerably since use started in 1922. The analogue insulins, as depicted above, which dominate current use, are the end product of this development. Earlier insulins are summarised briefly in section 5.1 (pgs 21-22) but are also examined in detail here.
Animal Insulin

Both bovine (beef) and porcine (pig) insulin were the initial insulins used clinically. They were extracted from the pancreata of these animals. Initially these mixtures were highly impure, pig insulin contained up to up 8% of porcine proinsulin material\textsuperscript{83, 84} but purity improved as re-crystallisation techniques were used. Gel and ion-exchange chromatography also improved the purity\textsuperscript{85-87}. Such insulin was short acting initially and it was not until the combination of insulin with Protamine or zinc that longer acting insulins were seen. This occurred in the 1930s and 40s. By the 1950s other substances were combined with insulin, such as globin, this also prolonged the action of these animal insulins\textsuperscript{88-92}. It was also noted that combining soluble (short acting) and long acting insulins could be done and in fixed ratios, the use of this ‘mixture’ could be clinically useful\textsuperscript{93}. The use of animal insulin either in fixed mixtures or free mixing of soluble and isophane insulin continued until the 1980s when the first ‘human’ insulin was produced.
Human Insulin

Human insulin was initially synthesised in semi-synthetic or biosynthetic forms. Semi-synthetic human insulin is made when porcine insulin is converted by the substitution of the amino-acid alanine by threonine at chain position B30\textsuperscript{94}. Biosynthetic human insulin is derived by one of two methods; enzymatic alteration of an intact human proinsulin gene inserted into a non-pathogenic strain of \textit{Escherichia coli}\textsuperscript{95} or from foreshortened synthetic proinsulin produced by genes which had been inserted in yeast\textsuperscript{96, 97}. The clinical transition to such insulin use occurred in the mid 1980s and it was not without controversy. Frequent reports of increased hypoglycaemia were seen\textsuperscript{98} and although it was thought to be a function of these insulins alone, it became apparent that this was not the case\textsuperscript{99, 100}. The use of these insulins still continues today, although in more recent years patients and healthcare professionals have often decided to change to the analogue insulins.

Human Analogue Insulin

As shown in the table above, there are now three short acting and two longer acting human insulin analogues commercially available. The short acting insulins have a decreased tendency to hexamer formation and so have a rapid absorption time. These analogues have specific amino-acid substitutions which lead to conformational and electrical changes within the molecule which decrease this hexamerisation\textsuperscript{101}. Insulin Lispro (Humalog, Eli-Lilly) swaps the positions of two amino acids, placing lysine at B28 and proline at B29\textsuperscript{102}. Insulin Aspart (Novorapid, Novo-Nordisk) replaces the proline at B28 with aspartic acid\textsuperscript{103, 104}. Insulin Glulisine (Apidra, Sanofi-Aventis) substitutes lysine at position B3 and glutamate at B29 to have its effect\textsuperscript{105}. All of these insulins are comparably faster than human insulin at being absorbed subcutaneously and so lend themselves well to the basal-bolus regime where rapid prandial insulin useful.
The two long acting insulins, Insulin glargine (Lantus, Sanofi-Aventis) and insulin detemir (Levemir, Novo-Nordisk) also have amino acid changes, but these differ considerably from the short acting insulins. Glargine has a diarginyl moiety added at B30 and glycine substituted at A21. This structure results in precipitation of the molecule at neutral pH, as found subcutaneously, and consequently a slower absorption\(^\text{106}\). Insulin detemir, meanwhile has a C14 fatty acid molecule, myristic acid, attached at B29 which consequently delays its absorption, giving it a nearly 24 hr duration of action as well\(^\text{107}\).

In comparison to the previously available insulins, the newer analogue insulins, rapid-acting ones having a fast onset and disposal and long-acting insulin having a more ‘peakless’ profile, could theoretically allow more aggressive dose titration to control blood sugars as the risk of hypoglycaemia would be reduced\(^\text{108}\). In clinical practice there is some evidence that the incidence of hypoglycaemia is lower on these newer insulins, although evidence of improved glycaemic control is less easy to demonstrate. Quality of life studies would suggest that the newer insulins are preferred by most patients\(^\text{20, 109, 110}\).

Restoring physiological insulin production- transplantation.

Whole pancreas and more recently Islet-cell transplantation have been explored as a form of permanent treatment for T1DM. Whole pancreas transplantation (WPT) as treatment for T1DM was first performed in 1966\(^\text{111}\). Due to poor graft survival, not many procedures were performed before 1978. However, by the year 2000 over 14000 transplantations had been performed worldwide, the increase in numbers being due in part to improved immunosuppressive therapies, improved surgical technique and better patient selection\(^\text{112}\). It is clear that graft survival is better when WPT occurs with simultaneous kidney transplantation for end-stage renal failure.
Less success is seen with lone WPT such that The American Diabetes Association only recommends this in patients with severe problems, such as

1) A history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycaemia, ketoacidosis) requiring medical attention;

2) Clinical and emotional problems with exogenous insulin therapy which are so severe as to be incapacitating;

3) Consistent failure of insulin-based management to prevent acute complications\textsuperscript{113}.

Islet cell transplantations were first performed in humans in the 1970s\textsuperscript{114}. The pancreatic islets are separated by digestion by a collagenase enzyme from pancreatic tissue\textsuperscript{115} and they are then subsequently purified. The islets comprise about 1.5\% by weight of the whole pancreas\textsuperscript{116}. Further attempts were made in the 1980s and 90s at Edmonton in Canada, but success was poor with insulin independence rarely reported\textsuperscript{117}. More recently these early failures, probably due to poor islet preparation and immunosuppression\textsuperscript{118}, have been improved upon\textsuperscript{119}. Islet cells are infused into the portal vein by the placement of a temporary catheter. The liver being chosen as the transplant site because it is highly vascular which favours graft implantation, and also because insulin would be secreted into the portal circulation, as in the non-diabetic individual\textsuperscript{118}.

Transplantation (WPT and islet) however, remains difficult with recognisable complications such as a surgical procedure, wound infection and graft failure for WPT implantation. Bleeding and portal vein thrombosis are the most common risks in islet transplantation. Both procedures also require the use of immunosuppressive therapy to prevent rejection and this can put patients at risk of infection and indeed increased incidence of malignancy. Whilst this remains a promising area of research and further studies are ongoing, for the majority of patients this is not a practical alternative to subcutaneous insulin treatment\textsuperscript{120-123}. 
5.4 Systems and Patients

The availability of technology such as sophisticated home blood glucose monitors to aid glucose control, the development of insulin analogues and the convenience of pen devices and finer needles to deliver insulin have all been major improvements toward the goal of improving glycaemic control over the past 10-20 years. Despite all these advances, their whole effectiveness depend on the patients with T1DM actively and consistently using these technologies to augment their care. Finally, the patient needs to be closely involved with their medical management and with a chronic disease such as T1DM this involvement and engagement is a lifelong commitment.

5.4.1 Systems of Diabetes Care

The delivery of diabetes care is an increasingly complex issue. When viewed globally many different health-care systems exist, but this thesis will concentrate on the systems delivering care in the United Kingdom.

Historically in the UK, most forms of health care are delivered within a tiered structure. Patient contact is generally initiated at the General Practitioner (GP). Referral, if required, is then made to secondary care services (usually a District General Hospital). Tertiary referral to ‘specialist’ centres occurs either directly from the GP or more usually from the DGH.

Over the last 60 years successive changes in Government have resulted in alterations of health policy (see table below). The more important changes are detailed following the table.
Table 5.4.1: Summary of key changes occurring in National Health Service (NHS) organisation since 1948.

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
<th>Legislation and Documentation</th>
</tr>
</thead>
</table>
| 2006 | Department of Health - Payment by Results  
National tariff 2006/07  
Strategic Health Authorities reduced from 28 to 10  
PCTs reduced to 151  
Supporting practice-based commissioning in 2006/07 by determining weighted capitation shares at practice level | Our Health, Our Care, Our Say  
Supporting people with long term conditions to Self Care |
| 2005 | Modernisation Agency replaced by NHS Institute for Improvement and Innovation.  
Department of Health - Treatment Centres  
Department of Health - Direct Payments | A Patient-led NHS  
Healthcare reform in England, Update and next steps. |
| 2004 | Patients Forums  
Commission for Healthcare Audit and Inspection  
First wave Foundation Trusts established | NHS Improvement Plan. |
| 2003 | Monitor established  
Patient Choice  
Community Health Councils abolished  
NHS Modernisation Agency  
Regional Directorates of Health and Social Care abolished | Building on the Best; Choice, Responsiveness and Equity in the NHS  
Health and Social Care (Community Health and Standards) Act |
| 2002 | Abolition of NHS regional offices  
Reorganisation of health authorities, from 96 to 28 strategic health authorities in England,  
Patient advisory and liaison services | Wanless report:  
National Health Service Reform and Health Care Professions Act  
Delivering the NHS Plan |
| 2000 | Abolition of the NHS Executive  
Primary Care Trusts (first wave) - eventually to reach 300  
National Service Frameworks | The NHS Plan |
| 1999 | Primary Care Groups (481)  
National Institute for Clinical Excellence  
Commission for Health Improvement  
Walk-in NHS Centres | Health Act  
Saving Lives: Our Healthier Nation |
<p>| 1998 | Abolition of GP fundholding | A First Class Service: Quality in the New NHS |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Community Fundholding</td>
<td>Health Service Commissioners (Amendment) Act Community Care (Direct Payments) Act</td>
</tr>
<tr>
<td>1991</td>
<td>Establishment of 57 NHS Trusts</td>
<td>Junior Doctors, the New Deal. Working Arrangements for Hospital Doctors and Dentists in Training</td>
</tr>
<tr>
<td></td>
<td>Reorganization of regional health authorities to reduce numbers from 14 to 8 regions.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GP Fundholding - 306 practices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Purchaser/provider split</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Department of Health and the Department of Social Security split</td>
<td>Community Health Councils</td>
</tr>
<tr>
<td>1986</td>
<td>NHS Management Board established</td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>General Managers appointed throughout the NHS</td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>Establishment of Regional Health Authorities and Area Health Authorities</td>
<td>&quot;Management arrangements for the reorganised NHS&quot; Democracy in the NHS</td>
</tr>
<tr>
<td></td>
<td>Community Health Councils</td>
<td></td>
</tr>
<tr>
<td>1949</td>
<td>Introduction of prescription charges</td>
<td>National Health Service (Amendment) Act</td>
</tr>
<tr>
<td>1948</td>
<td>5 July The appointed day- Beginning of the National Health Service</td>
<td>Children Act National Assistance Act</td>
</tr>
</tbody>
</table>

- General Practitioners were permitted to become fundholders in 1989; allowing them to purchase services, such as diabetes management, from any provider of that service.

- Subsequently, this policy was modified when fund holding was taken back to the Strategic Health Authority and Primary Care Trusts developed (2000). Also hospitals providing care became independent trusts i.e. not financially managed by the strategic health authority\(^{124}\).

- Further changes in health policy and the organisation of primary care provision occurred in 2004/2005 with the adoption of the General Medical Services (GMS) contract.
Many chronic diseases were structured under the Quality outcomes Framework (QoF) and diabetes care was included. Under this system primary care physicians have their income partially linked to achieving a series of outcome measures. With respect to diabetes care, factors such as HbA1c, Blood pressure, and screening of urine microalbumin-creatinine ratios were included. When the percentage of patients achieving the target values within a practice increased, so did the income. Clearly this performance-linked income could be used to drive improvements in the ‘care’ delivered\textsuperscript{125}.

Whether such moves have had an effect on clinical outcomes i.e. microvascular complications is unclear. There has however been a significant impact on the delivery of diabetes care as a result of these changes\textsuperscript{126, 127}.

For patients with T1DM early referral to secondary care services generally occurs, although some patients may have already presented, usually through metabolic decompensation, to hospital and will continue with this follow-up. Secondary care services usually supervise care and manage the patient as an outpatient, liaising with the GP. The nature of diabetes care has resulted in a ‘team’ of multi-disciplinary health-professionals developing within the diabetes speciality and delivering care in the form of a ‘Diabetes-Team’\textsuperscript{128}. Such teams generally include a Physician, Diabetes nurse specialist/educator, podiatrist and a dietician. A shared-care policy with the GP allows regular review of medication and management from both primary and secondary care\textsuperscript{129}.

In an effort to provide a similar standard of care nationally the government issued a National Service Framework (NSF) for Diabetes care in 2001. This aims to provide a series of agreed national standards of provision and delivery of care and eliminate any inequalities of care between areas\textsuperscript{130, 131}.
These changes have resulted in specialist diabetes teams adapting the services provided in an effort to evolve with the system. Some care teams now straddle the once clear delineation between community and secondary care by providing ‘Community Diabetes Consultants’ to provide education and training to primary care teams, oversee and develop referral pathways and to facilitate rapid referral to the specialist teams. Other teams have adapted by fine-tuning the services they provide to patients with diabetes, making referral pathways more structured and direct. Which model of care will prevail over the next few years is uncertain, but such changes do provide an exciting challenge for those teams aiming to provide excellent care for their patients with diabetes.

5.4.2 Patients with type 1 diabetes

Where does the patient with type 1 diabetes fit in with the changes seen in health policy, care-providers, technological developments and newer insulins? To simply provide a patient with insulin or other medication to treat their diabetes does not mean that their disease has been addressed. The care that is offered to patients has to be contextualised to take into account multiple factors. The American Diabetes Association (ADA) recommends that HbA1c targets are individualised. Indeed it may be appropriate to try and make all care targets individualised. What any one patient will understand in an education programme may not be understood by another, whilst one patient’s love of exercise may be the complete opposite of the sedentary or physically restricted patient.

In essence, as with all branches of medicine, a ‘package of care’ is not necessarily a one-size-fits-all solution for all patients. Diabetes teams have attempted to address such issues with a variety of different approaches to involve and engage the patient in their own care. Educational packages have developed to suit those who learn
more effectively in one-on-one sessions, as well as those who appreciate the value of peer group support. Specialist nurse care and physician outpatient contacts have evolved in an attempt to offer individual treatment and set individual goals. Part of this care is reliant on the therapeutic relationship and trust established over consecutive visits.

It is difficult to study the way a patient manages their diabetes in the ‘real-world’ as opposed to studying a patient in a time and goal defined clinical trial, particularly when you consider the myriad of factors which can impinge on their lives. In this thesis I have attempted to address some of the issues that patients face in the real world when managing their disease and how this can influence the outcome of their care.

I have examined some of these issues using data obtained from a secondary care outpatient diabetes clinic for adults with T1DM, who have had continued contact with the same consultant diabetologist and diabetes specialist nurse over the period of their care. The data has been compared with those patients in the landmark clinical trial for T1DM, the DCCT, to assess whether a real-world group of patients can achieve similar results.

The clinical follow-up of this patient cohort has spanned many of the changes discussed in this introduction. I have therefore re-examined their care in the light of some of the more recent changes and attempted to assess the impact of them on measurable outcomes. Some of the challenges of inpatient diabetes care are also discussed. This is an increasing area of interest in diabetes care, the evidence suggesting that the percentage of hospital in-patients with diabetes is rising and that the care of these patients could be improved.

Finally, the complex nature of factors external to diabetes and how they affect T1DM is examined in patients with both T1DM and problems with intravenous drug abuse.
This appears to be an increasing problem, not just intravenous drug use, but recreational drug use as a whole- within the general population and young adults predominate. Young adults with T1DM are therefore as likely to use recreational drugs as the non-diabetic population. Recent studies have further high-lighted this issue\textsuperscript{139-142}. Demonstrating issues with overall control, but also the incidence and prevalence of metabolic decompensation. This can clearly impact on general diabetes care and control, particularly with young adults, and so this issue is described within the thesis.
6. Literature review
This thesis examines the importance of and challenges to achieving good glycaemic control in a population of patients with type 1 diabetes. It also studies the prevalence of cardiovascular risk factors and the achievement of management targets in the same population, as well as appraising the factors, which in the ‘real-world’ limit the ability to achieve these goals. A review of the literature concerning these issues is therefore important.

**Diabetes Control and Clinical Outcomes**

_The Diabetes Control and Complications Trial_\(^4\)

Modern diabetes care attempts to achieve a normal lifespan free from complications for patients with this disease. The landmark trial, the DCCT, set the precedent in T1DM demonstrating that glycaemic control was associated with microvascular disease outcomes.

In a randomised control trial of 1441 patients aged 13-39 years of age recruited between 1983 -1989 (see Table 6.1 for detail) half the patients received intensive therapy and half standard therapy. Each treatment arm was subdivided into two groups, a primary prevention half (no evidence of retinopathy or microalbuminuria at enrolment) and the secondary intervention half (mild to moderate retinopathy and/or microalbuminuria, but not macroalbuminuria).

Those receiving intensive treatment; 4 injections a day or continuous subcutaneous insulin (CSII) and a minimum of 4 self monitoring blood glucose tests a day as well as aiming for an HbA1c <6.05%, had better outcomes than those on the standard therapy of 2 injections a day and self monitoring by urine glucose tests.
After almost 7 years of follow-up the average HbA1c was 7.3% in the intensive arm and 9.1% in the standard arm. 99% of the patients completed the study (11 deaths, 32 deemed inactive status (patients who withdrew or were deemed unfit to continue the study by a physician), including 8 lost to follow-up).

Main findings

For those patients on intensive treatment compared to conventional treatment:

- 76% reduction in appearance of new retinopathy (1° prevention)
- 54% reduction in progression of retinopathy (2° intervention)
- 34% reduction in development of microalbuminuria (1° prevention)
- 43% reduction in microalbuminuria and 56% reduction in macroalbuminuria (2° intervention)
- 69% reduction in appearance of neuropathy at 5yrs (1° prevention)
- 57% reduction in appearance of neuropathy at 5yrs (2° intervention)
Many of the principles behind this study arose out of the groundwork laid in earlier studies in patients with T1DM including, the STENO study\textsuperscript{25,143}, and the KROC collaborative study group\textsuperscript{144,145} the findings of which demonstrated that improved glycaemic control might have an impact on the development of microvascular disease. However, the DCCT proved this definitively with large numbers of patients. It is important to recognise though, that the patients recruited to this trial were not wholly typical of the general population with T1DM. This group were a highly motivated selection of volunteers who had an interest in self-care. Patients with other diseases were excluded. The rate of smoking in this group did not perhaps reflect that of the general population\textsuperscript{146}. The mean age of the all the patients was 27 years, whilst the mean duration of diabetes was short in the primary prevention arm (2.6 ±1.4 years) and quite short in the secondary intervention arm (8.9±1.5 years). Additionally, the patients on the intensive arm of the study received a great deal of input to help them achieve their targets, including weekly specialist nurse input and monthly physician review. In summary the comparison between these patients and those in the ‘real-world’ is not ideal.

*The Epidemiology of Diabetes Interventions and Complications trial*\textsuperscript{147}

Subsequent to the completion of the DCCT, the majority of the patients in the study continued to be followed up in the EDIC\textsuperscript{147} (Epidemiology of Diabetes Interventions and Complications) study, 1425 patients from DCCT were invited, 1375 (96%) agreed to participate.
In this study the patients, after discussion with their care providers, adopted the most suitable insulin regime for them. They were however, encouraged to adopt the intensive treatment regime used in the DCCT. Within 2 years 69% of the previous standard treatment group were using the intensive regime or CSII therapy, while 95% of the former intensive arm patients continued with the same treatment\textsuperscript{147}. By 4 years of follow-up the average HbA1c of the two former patient groups were no longer significantly different and averaged around 8%. However, the previous intensive group patients still had significantly lower levels of retinopathy and nephropathy than the former standard therapy patients. The prevalence of hypertension, closely linked to nephropathy, was the same in the two groups at the end of DCCT, but by 6 years into EDIC it was significantly higher in the patients previously on standard therapy. The benefits gained from a period of intensive glycaemic control seem to persist for years after and are demonstrated well in this group of patients followed up in EDIC\textsuperscript{148}. Compelling evidence for the benefits of intensive glycaemic control such as this would support its’ adoption into routine clinical practice.

\textit{Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes}\textsuperscript{36}

As both DCCT and EDIC demonstrated the benefits of intensive insulin therapy and good glycaemic control in preventing microvascular disease, it was thought a similar effect would be seen in the prevention of cardiovascular disease. Unfortunately, both studies initially failed to demonstrate such a benefit, although a trend towards improvement was suggested. This was attributed to the age of the patients and the duration of disease during these studies. Therefore the same DCCT/EDIC cohort was reviewed again in 2005 to examine whether any effect on the incidence of cardiovascular disease could be seen, and if good glycaemic control influenced this.
Of the 1441 patients originally recruited to DCCT, 93% (1341 pts) were followed until February 2005. Cardiovascular disease was defined as non-fatal myocardial infarction, stroke, death from cardiovascular disease, confirmed angina and/or the need for coronary-artery revascularisation. At the time of re-review the mean duration of follow-up was 17 years. The mean duration of diabetes was 28 years. During this time 46 cardiovascular disease events occurred in 31 patients from the former intensively controlled group, compared to 98 events in 52 patients from the conventional control group.

On analysis, intensive treatment reduced the risk of any cardiovascular event by 42% (p=0.02) and the risk of non-fatal myocardial infarction, stroke or death from cardiovascular disease by 57% (p=0.02).

The decrease in HbA1c that occurred during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease. Meanwhile the presence of microalbuminuria and albuminuria were associated with a significantly increased risk of cardiovascular disease. The differences between the two groups remained even after adjusting for these factors.

This study was important as it demonstrated something that, although suspected had not been fully proven in other trials. Cardiovascular disease is not specific to T1DM, but patients with the disease do show rates 10 fold that of an age matched population without diabetes. It also demonstrated that the traditional risk factors (Smoking, higher body-mass index, higher total and LDL cholesterol) were all associated with the development of cardiovascular disease, adding further weight to the argument in favour of addressing these risk factors early in the duration of T1DM.
**Limiting Factors to achieving good Diabetes Control.**

These two studies demonstrate the benefits of intensive diabetes control in the prevention of microvascular disease. The latter study (EDIC) also shows that without the previous high levels of support seen in the DCCT even a trial population struggle to maintain glycaemic control close to the DCCT targets. Equally, it also shows that patients who were less well controlled can improve their control with physician advice and a more intensive insulin regime. The challenge to health professionals and patients is to achieve good glycaemic control with limited time and resources whilst facing other factors in a non-clinical trial world, which affect how a patient with diabetes manages their condition.

*Translating the DCCT into clinical practice; overcoming the barriers*\(^{149}\)

The adoption of the principle of tight glycaemic control into everyday practice is not without difficulty; as described in this paper\(^{149}\). It discusses the potential barriers to success and identifies the following areas where such difficulty may occur.

**Barriers within the therapeutic regimen to achieving good diabetic control.**

Frequent capillary blood glucose monitoring
Need to monitor carbohydrate intake.

**The Barriers within the healthcare team to achieving good diabetic control.**

The need for a unified message
Open and ongoing communication with the patient

**The Barriers within the patient to achieving good diabetic control.**

Include motivation
Personal and professional support
The risk of hypoglycaemia.
Addressing these issues in clinical practice, even shortly after the publication of the DCCT was an important aspect of diabetes care that many teams appreciated. Hypoglycaemia and weight gain were identified as two of the more obvious factors which may limit the ability of both the patient and the care team to achieve good glycaemic control.

**Hypoglycaemia, Insulin use and weight gain.**

*Hypoglycaemia in the Diabetes Control and Complications Trial*\(^{150}\)

This paper, published in 1997, described the problems of intensive insulin regimes within the trial; 65% of the intensive control group having had at least one severe episode of hypoglycaemia compared to only 35% of the conventional control group. This gave a relative risk of 3.28 of severe hypoglycaemia with intensive control. Males and those with previous episodes of hypoglycaemia were at particularly high risk. Within both groups patients who had experienced severe hypoglycaemia were at increased risk of subsequent episodes.

Hypoglycaemia is a much feared complication of insulin use by the patient and is well described by M\(^{\text{c}}\)Crimmon and Fryer\(^{151}\).

Hypoglycaemia has also been associated with an increased dietary intake in the hours following such an event. The dietary choices also appear to be poor, predominantly consisting of fat and carbohydrate heavy foodstuffs\(^{152}\). It is not unreasonable to suggest that intensive insulin regimes, using higher doses of insulin, can lead to weight gain through simple insulin use, but also secondary to increased hypoglycaemia and subsequent calorie laden food choices thereafter.
Influence of Intensive Diabetes Treatment on Body Weight and Composition of Adults With Type 1 Diabetes in the Diabetes Control and Complications Trial 153

This review of the DCCT patients demonstrates that weight gain is a recognised complication of intensive therapy. A weight gain of an average of 4.75kg in the intensive arm compared to the conventional arm is a factor that both clinicians and patients are aware of.

Patients, particularly young female patients, can be very conscious of weight gain and may subsequently indulge in behaviours to avoid it. Eating disorders have been reported to be more prominent in young female patients with T1DM than in the general population154, 155, although some studies fail to demonstrate this finding consistently156. It is clear however, that there is an element of disordered eating amongst many individuals with T1DM157-159. The reasons for this are not entirely clear, but weight control is a factor to consider in these people, particularly with regards to insulin use- or more correctly, under-use. Relative omission of insulin not only restricts weight gain but also results in sub-optimal glycaemic control.

Non-compliance and non-attendance; their potential causes.

DARTS/MEMO collaboration Adherence to insulin treatment, glycaemic control and ketoacidosis in insulin dependent diabetes mellitus160

This study highlighted the fact that 28% of the patients (n=89) reviewed did not take the prescribed insulin dose. Those who omitted insulin were shown to have poorer glycaemic control and more admissions to hospital with ketoacidosis. These patients were young adults with a mean age of 16 and although it is difficult to identify formally such behaviours in older groups, it is possible they occur. It is also not unexpected to find people who omit insulin and have sub-optimal glycaemic control.
are less likely to attend outpatient clinic appointments, than those more motivated to do so.

Lost to follow-up: the Problem of Defaulters from Diabetes Clinics

This paper reviews the research regarding defaulters from the diabetes clinics. It is estimated that between 4-18% of patients default from English hospital clinics although this can range up to 40% in some clinics. Various factors have been identified to be associated with non-attendance. They are usefully classified as in the table 6.1.

By identifying some of the factors associated with clinic non-attendance it then becomes possible to address them and potentially improve clinic attendance rates. The paper then goes on to examine some of the methods which could, or indeed have been, employed in reducing non-attendance rates, categorising them as interventions as shown in table 6.2

Table 6.1 Classification of reasons for clinic defaulting (taken from Griffin)

<table>
<thead>
<tr>
<th>Patient Socio-demographic features</th>
<th>Patient Clinical Features</th>
<th>Features of the Appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Age</td>
<td>Doctor Identified</td>
<td>Long intervals to</td>
</tr>
<tr>
<td>Male gender</td>
<td>psychological problems</td>
<td>appointment</td>
</tr>
<tr>
<td>Low socio-economic status</td>
<td>Low knowledge about</td>
<td>Previous non-attendance</td>
</tr>
<tr>
<td>Low educational level</td>
<td>disease</td>
<td>Time of appointment</td>
</tr>
<tr>
<td></td>
<td>Health beliefs</td>
<td>Patient satisfaction with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the consultation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient satisfaction with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>health professional</td>
</tr>
</tbody>
</table>

Some of these interventions have been adopted in diabetes clinics in an effort to reduce non-attendance rates. Encouraging patients to attend clinic is important as
evidence suggests that non-attendance is associated with adverse patient outcomes\textsuperscript{162,163}. Two factors frequently cited as underlying reasons for non-attendance, as well as being associated with poor outcomes generally, are those of socioeconomic status and education.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Organisational</th>
<th>Professional-patient communication</th>
<th>Other Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailed clinic reminders</td>
<td>Individualised clinic times</td>
<td>Patient led consultations,</td>
<td>Improved communication between primary and secondary care</td>
</tr>
<tr>
<td>Phone call reminders</td>
<td>Physician continuity</td>
<td>Patient centred care</td>
<td></td>
</tr>
<tr>
<td>Highlighting the consequences of non-attendance</td>
<td>Efficient and contemporary register and recall systems</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6.2 Interventions to improve clinic attendance (from Griffin)

The influence of socio-economic status and educational attainment on glycaemic control.

There have been a number of papers reporting the association between socio-economic status (SES) and glycaemic control. There remains a problem however in how socioeconomic groupings are defined. There is some variation between reports from different countries. However, the general interpretation of such data suggests that in patients who have lower SES tend towards poorer glycaemic control\textsuperscript{164-166}. Not only that, but the prevalence of microvascular disease and the risk of acute metabolic complications also appear to be higher\textsuperscript{164}. The association of macrovascular disease with SES in these patients with T1DM is less clear-cut though, despite higher prevalence rates for smoking and higher cholesterol values when compared to those of higher SES\textsuperscript{167}. 
The role of socioeconomic status, depression, quality of life, and glycaemic control in type 1 diabetes mellitus.\textsuperscript{165}

A cohort of 222 patients with T1DM aged 8-17 was studied and the relationship of SES of the patients’ parents/guardians and HbA1c, as well as examining other psychosocial factors was examined. It demonstrated a 1.5x greater risk of poor glycaemic control in those with lower SES than those with a high SES.

Relationship between glycaemic control, ethnicity and socioeconomic status in Hispanic and white non-Hispanic youths with type 1 diabetes mellitus\textsuperscript{168}

In a study of 183 patients aged 21 or less with T1DM in New Mexico, compared glycaemic control with ethnicity and SES\textsuperscript{168}. The results suggested, that when comparing ethnic differences (Hispanic vs White non-Hispanic), a significant association with HbA1c could be found, the Hispanic group having a slightly higher HbA1c (8.8% v 8.3%, p=0.03). When comparing all the variables using analysis of variance however, only SES demonstrated statistical significance. Those patients/families with a lower SES had significantly higher HbA1c than those patients in higher SES groups.

Educational status- that is level of educational attainment- is closely linked with SES, and it is this relationship that has made the direct association of either SES or education with glycaemic control difficult. A study was done of 2387 patients with T1DM who were part of the EURODIAB-IDDM\textsuperscript{169} study and it examined the relationship between educational attainment and glycaemic control\textsuperscript{164}. Those patients with only a primary education had poorer glycaemic control than those who had received a college education. The association with unhealthy lifestyles e.g. smoking and little exercise was also stronger in the primary education group.

Socioeconomic status and educational attainment may be factors influencing the glycaemic control of patients with T1DM and this may be because both factors are
involved in the motivation of such patients to address their health needs. Addressing these areas is something which may bring long-term benefit in many aspect of a patients’ health, including glycaemic control, but the remit for this is on a political or even a public health platform and not necessarily during an outpatient consultation. The factors which can be influenced are often those that both the doctor and the patient perceive to be the major obstacles to good glycaemic control and are commonly those mentioned earlier such as hypoglycaemia, weight gain and dietary management. Many of the developments within the diabetes speciality such as analogue insulins, continuous glucose monitoring, carbohydrate counting and DAFNE courses for example, have focussed on addressing these areas.

**Insulin formulations and glycaemic control**

**Long acting (basal) insulin**

Insulin use is associated with a risk of hypoglycaemia. This risk is higher with intensive insulin regimes. To address this, newer insulins have been developed with reputedly more predictable time action profiles, for example Glargine, and Detemir\(^{106,170}\). Theoretically these insulins can be more intensively titrated without an increasing risk of hypoglycaemia, therefore allowing better glycaemic control. Certainly, with regards to insulin Glargine, clinical trials have demonstrated both a lowering of HbA1c and less frequent hypoglycaemia\(^{171-173}\) and although direct clinical experience does not fully reinforce the trial data, less hypoglycaemia is certainly seen in the real world than with the use of NPH insulin\(^{174,175}\). Insulin Detemir, marketed after Glargine, also claimed similar properties with reduced hypoglycaemia compared to NPH insulin\(^{171}\) but with the added benefit of not causing significant weight gain. The clinical evidence for this is smaller than with glargine in patients with T1DM\(^{176,177}\). Detemir with its shorter half-life has been used twice daily
and has been shown to be effective, although use of once daily dosing also appears to be as effective\textsuperscript{178}. The weight neutrality of its use does lend it an advantage and various theories have been raised as to why this occurs in comparison to other insulins. The main theories suggest that as Detemir preferentially binds with albumin in the circulation, it is predominantly associated with an effect on the liver, rather than in the periphery, limiting hepatic glucogenesis\textsuperscript{179}. Other work carried out in patients with type 2 diabetes, suggests it may also act as an agent in influencing satiety because of its ability to cross the blood-brain barrier\textsuperscript{179, 180} and exert its’ effect on the central satiety centres. It therefore remains useful in the clinical setting and serves as an option for both doctor and patient in addressing both weight control issues and hypoglycaemia.

**Short-acting (mealtime) insulin**

The short acting analogue insulins have also been useful in addressing hypoglycaemia and stabilising glucose control around mealtimes in comparison to the older short acting insulins. The two most frequently used short acting analogues are Insulin Aspart (Novorapid) and Insulin Lispro (Humalog).

**Insulin Lispro (Humalog)**

Insulin Lispro improved post prandial glucose control at the expense of an increase in fasting and-pre prandial levels in comparison with soluble insulin when used as part of an intensive regime with NPH insulin used as the basal therapy\textsuperscript{181}.

Improvements in post prandial glucose variation and HbA1c occurred when using Lispro compared with normal human insulin and NPH in a multicentre, 32 week, cross-over study\textsuperscript{109}. The rate of hypoglycaemia was also reduced in this group. Patients have also report improved quality of life using analogue insulin. In a study of 770 patients in an open label trial for 12 weeks, quality of life was assessed before and after a change in therapy\textsuperscript{182}. Statistically significant improvements in
insulin therapy related quality of life scores were seen, as well as improved HbA1c, without an increase in hypoglycaemia.

**Insulin Aspart (Novorapid)**

In a multicentre study of 90 patients with T1DM, insulin Aspart reduced excursions of glucose outside a predefined range in comparison to soluble human insulin. It also significantly reduced post prandial hypo and hyperglycaemia\(^\text{183}\).

Improvements in data regarding HbA1c are small at best but data on the quality of life with the new insulins are well described. A randomised, multi-national open label trial of insulin aspart vs normal insulin for 424 patients on an intensified insulin regime has reported\(^\text{184}\). It compared outcomes in quality of life and treatment satisfaction between the two groups (2:1 ratio) over a six month period and concluded that under study conditions, aspart improved treatment satisfaction and quality of life regarding diet restrictions when compared with human insulin. This was mainly reflected by improved satisfaction with increased dietary and leisure time flexibility.

Changing from human insulin to analogue insulin does seem to show benefit in terms of tighter glycaemic control and smaller post-prandial variations, as well as improved quality of life scores. Similar questions of improvement have been raised over the method of insulin delivery.
Continuous subcutaneous insulin infusion devices (Insulin pumps)

An intensified insulin regime by multiple dose injection can be effective at controlling diabetes but has the disadvantage of requiring multiple daily injections. An alternative method of insulin delivery is the insulin pump. Here continuous subcutaneous insulin infusion (CSII) is the method of delivery and depends on regular monitoring and adjustment of the infusion rates around meals and exercise. The pump method has been popular for many years but its use in the UK has been lower than its use in other countries\textsuperscript{185}, an estimate putting use in the UK at ~1% of patients with T1DM compared to countries such as USA where up to 20% of patients with T1DM may use pumps. There have been, particularly in the past, many barriers to pump use in UK and they include:

- Availability of financial resources
- Suitable trained health-professionals to supervise use
- Lack of knowledge about the effectiveness of CSII.

There are also differing opinions about who is suitable for pump use. When considering a patient for use of an insulin pump, several factors need to be considered. These include cost, lifestyle, technical expertise, differing complications encountered between MDI and CSII, achievement of normal glucose concentration and diurnal blood glucose variation. The relative merits of MDI and CSII are described well in an editorial\textsuperscript{186}, and are illustrated below.
Table 6.3—Advantages and disadvantages of MDI versus CSII. (from Schade DS, Valentine V. To pump or not to pump. Diabetes Care 2002;25:2100-2)

<table>
<thead>
<tr>
<th>Consideration</th>
<th>MDI</th>
<th>CSII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of therapy</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Lifestyle flexibility</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Technical expertise</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Complications of therapy</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Glucose normalization</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Decreased glucose variability</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

The evidence of benefit in favour of CSII or MDI depends a little on which parameters are examined. Quality of life measures appear to improve in those people who change from MDI to CSII\textsuperscript{41,187} although this may be age dependent and not all evidence supports this claim\textsuperscript{188}. Improvements in HbA1c are seen with pump use but they remain marginal when compared to an optimised MDI regime using analogue basal and bolus insulin\textsuperscript{189}.

There appears to be one clear benefit though in the use of CSII and that is the reduction in hypoglycaemia\textsuperscript{42} which is repeatedly reported. This was more readily observed in comparison to regimes not using analogue insulin but still appears to remain. What also remains is a risk of developing DKA whilst using CSII, which may be higher than those on an MDI regime\textsuperscript{190} and this must be considered before initiating a patient on CSII. However, the treatment does appear to be safe and effective in certain groups of patients with T1DM and this has been recognised recently with a re-appraisal by the National Institute for Health and Clinical Excellence (NICE) of pump technology use in T1DM\textsuperscript{191}. It would seem that the
flexibility that CSII allows coupled with smaller overall insulin doses and less apparent hypoglycaemia, could result in benefits in more patients with T1DM than we currently see in the UK.

The insulin pump may not the way forward for all patients; for those for whom the pump is unsuitable, or who opt to stay with injections, then intensive insulin therapy in the form of MDI remains the treatment of choice. However, as discussed earlier, this regime carries with it the potential problem of weight gain.

**Addressing weight gain in patients with T1DM**

Methods of addressing weight gain in people with diabetes include dietary control, exercise or medication such as metformin or anti-obesity medication.

**Dietary strategies to aid weight control**

This area seems to have come full circle in the 85 years since insulin was first used. Dietary management was the only way to palliate patients with T1DM prior to the discovery of insulin. Clearly such strict regimes as advocated in the 1920s are no longer relevant. More recently however, a number of different approaches have attempted to guide patients in dietary manipulation to limit glucose excursions and the potential for weight gain.

**Dose Adjustment for Normal Eating (DAFNE)**

DAFNE\(^2\) is a strategy that was developed to allow dietary freedom whilst using intensive insulin treatment in patients with T1DM. The results of this study showed no significant increase in weight, despite an increase in insulin injections and total daily dose. The group assigned to dose adjustment also showed small but
significant improvements in HbA1c at 12 months. Improvements in quality of life between baseline and endpoint were also noted.

Other suggested dietary strategies include the use of preferential low glycaemic index carbohydrates within the standard dietary advice given to patients with diabetes. The idea being that post-prandial hyperglycaemia is limited in comparison to normal dietary carbohydrates. The experimental evidence for this in T1DM is small and suggests only minor improvements in post-prandial glucose changes, with no real significant changes in HbA1c compared to the standard dose. In many of these studies weight change was not observed\textsuperscript{193, 194}. Theoretically, post-prandial glucose surges can lead to increased fat deposition and weight gain, so these were disappointing results.

**Exercise strategies to aid weight control**

Physical exercise is a method to help control weight gain in patients. Regular exercise in patients with T1DM is recommended in clinical practice guidelines\textsuperscript{195-200}. Studies would suggest that in general these recommendations are not met by most patients\textsuperscript{201}, but clearly exercise is beneficial in controlling weight and other cardiovascular risk factors. In a study of a moderately well controlled group of 20 patients, it was shown that regular (>135 mins/week for 3 months) endurance-type exercise led to a decrease in LDL-C, systolic and diastolic blood pressure, waist-hip ratio, total body fat and body weight. Increases in HDL-C and lean body mass were also seen\textsuperscript{202}. These changes occurred independently of changes in glycaemic control and there was no significant increase in the incidence of hypoglycaemia. Another observational study of 141 patients with T1DM showed a positive correlation between aerobic capacity and lean body mass and hand-grip strength. Aerobic capacity was negatively correlated with duration of diabetes, fat mass and BMI. Interestingly, there was also a weakly positive but statistically significant
correlation between aerobic capacity and HbA1c. The authors concluded that this higher HbA1c in patients with higher aerobic capacity may be a function of permissive hyperglycaemia practiced to prevent hypoglycaemia during or shortly after exercise.

**Medication based strategies to aid weight control**

If diet and exercise cannot limit the weight gain associated with insulin use then additional medication may be a treatment option. There are propriety weight-loss medications available via prescription and these are often used in the treatment of obesity and type 2 diabetes. These are currently Orlistat and Sibutramine in the UK. The literature on these is extensive and is not particularly relevant to patients with T1DM and will not be addressed here. However, other medication is being increasingly used in an attempt to restrict insulin associated weight gain, or aid weight loss in T1DM. Those of particular interest are Metformin and Pramlintide.

**Metformin**

Metformin, a biguanide which acts to increase glucose uptake in the liver and increase peripheral insulin sensitivity, is more commonly used in type 2 diabetes. In recent years it has been trialled in patients with T1DM who appear to have a degree of insulin resistance, or who are having issues with insulin associated weight gain. As early as 1985 metformin was noted to improve insulin sensitivity in patients with T1DM. This resulted in small trials to assess if glycaemic control could also be improved. Clinical use of metformin has continued and is further supported by more recent data. In an open label trial of 16 patients aged between 18-40yrs, using metformin at doses of 500-850mg twice daily, the authors observed improvements in insulin sensitivity and total daily insulin dose after 3 months. They then later conducted a retrospective analysis of patients who remained on insulin with additional metformin for up to 2 years. These patients showed initial improvement in
HbA1c- which decreased with duration of therapy, but also increased quality of life and decreased BMI\textsuperscript{208}.

Further studies of prolonged use of additional metformin in T1DM in normal clinical practice are needed to give a clearer picture of its' sustained benefit.

**Pramlintide**

Pramlintide is a synthetic replacement of the beta-cell hormone amylin. Amylin secretion, like insulin secretion, is lost as the beta cells are destroyed. Amylin has been shown to have gluco-regulatory effects which complement the effects of insulin. These include suppression of post-prandial glucagon secretion and delaying gastric emptying. Replacing amylin deficiency with the synthetic analogue Pramlintide has been show to reproduce these effects. It was therefore felt that if pramlintide were added to insulin therapy in patients with T1DM additional benefits may be gained.

In a double blind, placebo controlled, parallel group, multicentre study of 651 patients with T1DM\textsuperscript{209}. Subjects were randomised to either placebo or pramlintide injections in addition to insulin therapy for 52 weeks. Pramlintide was given as 60mcg subcutaneous injections either three or four times a day. By the end of the study HbA1c had reduced by 0.29% and 0.34% in the 3 and 4 times a day injections respectively, compared with 0.04% in the placebo group. This reduction in HbA1c occurred without an increase in insulin use. A significant reduction in body weight of 0.4kg occurred in both study arms, compared to a 0.8kg gain in the placebo arm. When these weight changes were examined in more detail, with reference to BMI at recruitment, it demonstrated that weight gain was prevented in lean patients, whilst it induced weight loss in the obese or overweight patients. There appears to be an effect on weight loss. However some critics have cited the increased rate of nausea associated with initial pramlintide use as being a major contributing factor in the
observed weight loss. The rate of nausea was approximately twice the rate of the placebo group in this study.

Further studies have subsequently been performed and notably patient satisfaction with pramlintide use has been assessed\textsuperscript{210}. During this trial of 29 weeks duration on 266 patients (130 pramlintide, 136 placebo) treatment satisfaction with pramlintide was reported. HbA1c decreased in both arms of the trial with no statistical significance between them; however weight fell by a mean value of 1.5kg in the pramlintide arm, while placebo treated patients gained a mean of 1.28kg. Other studies have shown similar small benefits\textsuperscript{211}.

Adjunctive treatments and newer insulins, educational input, diet and exercise and additionally improving the way the diabetes outpatient service is structured and delivered can all potentially improve clinic attendance and glycaemic control, with the aim of reducing the microvascular complications of diabetes. Increasingly clinicians have been attempting to address the macrovascular disease seen in patients with T1DM.

**Macrovascular disease in T1DM**

The traditional risk factors for macrovascular disease (Blood pressure, smoking and serum cholesterol) have been addressed aggressively, often attempting to achieve the targets recommended by various professional bodies\textsuperscript{34, 212}. Success had been variable and has focused mostly on patients with type 2 diabetes\textsuperscript{201}. Care targets for patients with T1DM have often followed those set for patients with T2DM. In general for the majority of patients care is still below the desired targets. The reasons for this are numerous but include many of the issues which affect achievement of glycaemic targets and attendance at clinics already highlighted in this literature review. Glycaemic control has been clearly associated with microvascular disease and
certainly, it has been know that there is an association between HbA1c and surrogate markers of macrovascular disease, such as coronary artery calcification, or carotid intima thickness, but until recently, hard evidence has not been available for a direct relationship with macrovascular disease.

**T1DM and Inpatient care**

Most of the care for patients with T1DM is delivered in an outpatient setting, but there are still a proportion of patients for which care is delivered as an inpatient. These cases are usually due to a metabolic deterioration requiring a short admission. Admissions can also be due to clinical issues which occur as a result of diabetic complications or medication use. The number of these admissions is clearly small in terms of the hospital population with diabetes, as patients with type 2 diabetes predominate. However, it is increasing\(^{213, 214}\). Patients with diabetes are recognised to have a longer length of stay in hospital than people without diabetes\(^{215, 216}\). Without specialist input, in the form of either diabetes specialist nurses or a diabetologist, patients continue to have a longer stay and therefore a more costly admission. Attendance by the specialist service decreases length of stay, reduces expenditure, aids follow-up and facilitates all round care\(^{134, 217-220}\). Even the management of the commonest metabolic disturbance resulting in admission, diabetic ketoacidosis, is under-managed by non-specialists. The introduction of care pathways has standardised care\(^{221, 222}\) and resulted in more accurate fluid and potassium replacement for these patients, attendance by specialists during the admission also facilitates education on sick day rules.

Improving care for both hospital inpatients and outpatients with T1DM remains the focus of diabetes care teams. Recently, inpatient care has been the subject of a major review by three of the leading professional bodies; the American Diabetes
Association (ADA) and the American Association of Clinical Endocrinologists
(AACE) and Diabetes UK (DUK), who have issued consensus statements regarding
inpatient glycaemic control\textsuperscript{2,223}. The chapters that follow in this thesis serve to
illustrate these areas further and expand our knowledge of the outcomes and follow-up of a cohort of patients with T1DM.
7. **Social setting, Clinic and Patients.**
As discussed in the introduction, much of the care patients with diabetes receive is best considered within the social setting they receive it. Primarily, this is because it has a bearing on their educational aspirations, their attitude towards chronic disease and their risk of other co-existent disease. A socially deprived area is likely to have a higher proportion of the population with other risk factors for cardio-vascular disease such as smoking, as well as lower educational attainment and lower long term health goals. When this is compared to a predominantly socially advantaged area where educational and health goals are high and motivation for good quality self-care is present, then differences are likely to be seen between the two groups.

The diabetes clinic which our patients attended sits in a unique position within the city of Liverpool. Unusually, it is attended by populations from three different Primary Care Trusts (PCTs), that is Sefton PCT, Knowsley PCT and Liverpool PCT. An area map is given below (Fig 7.1).

![Map showing position of the Walton Diabetes Centre (A)](image)
7.1 Sefton PCT

The area covered by Sefton PCT (North of Liverpool city centre) is shown in the diagrams below.

Denotes the position of Walton Diabetes Clinic

The population north of Formby primarily attend the Hospital trust based in Southport to receive their diabetes care as this is the closest local hospital, although some patients do attend the Walton diabetes clinic. The area between Maghull and Crosby and towards Bootle, fall under the catchment area of our clinic. The middle area, south of Formby running to Crosby-Maghull can choose- as indeed any patient can- to attend either hospital.

This is relevant when viewing the demographic data on these areas. The area surrounding Bootle and running to the edge of the district towards the location of the diabetes clinic contain seven electoral wards which fall into the most 25% deprived electoral wards in England. As evidenced here in the wards circled above. These areas have a significantly lower life expectancy when compared to the most affluent.
areas (shown in white and light blue) 74.6yrs v 80.6 yrs. In other markers Sefton generally performs poorly. Additionally it has significantly worse rates for poor quality housing, binge drinking, low levels of healthy eating, deaths from smoking, early deaths from cancer, alcohol related hospital stays, drug misuse treatment and importantly, significantly more people with diabetes than the average for England as a whole\textsuperscript{224}. 
7.2 Knowsley PCT

The area covered by Knowsley PCT (East of Liverpool city centre) is illustrated in the diagrams below.

- Denotes the position of Walton Diabetes Clinic

The area within the PCT from which patients most commonly attend the diabetes service where our clinic is based is predominantly, but not exclusively, above the dashed line. Below the line the population tends to attend the diabetes service based at the hospital just outside Prescot.

Much as with the previously described PCT, there are differences within Knowsley with regards to health. The figure above illustrates the deprived areas within the PCT. The darker the colour, the more deprived. Many of the electoral wards fall into the 25% most deprived wards in England. Life expectancy is lower than the national average in both men (73.6yrs) and women (78.2yrs).
Knowsley is also worse than the national averages in the following variables: GCSE examination achievements (5 A-C), smoking, binge drinking, healthy eating, deaths from smoking, cardiovascular disease and cancer, alcohol related hospital stays, drug misuse, tooth decay and the prevalence of diabetes \(^{225}\).
7.3 Liverpool PCT

The last PCT which acts as a feeder of patients to the diabetes centre, in which our clinic is based, is Liverpool PCT; the area it covers is shown below.

- Denotes the position of Walton Diabetes Clinic

The dotted line demonstrates the proportion of the PCT that commonly attend our diabetes clinic, areas below this line are more likely to attend the hospital based in the centre of Liverpool.

Men can expect to live 73.2 and women 77.9 years in Liverpool, less than both the regional and national average and for women, the lowest life expectancy in England. Deprivation scores are also high. The coloured figure above shows the degree of deprivation, 24 out of 28 electoral wards are in the 25% most deprived wards in England. Liverpool PCT, in common with the other PCTs already described scores low in a number of variables when compared to the national averages. Such areas include: poor quality housing, poor educational achievement, more violent crime,
smoking and binge drinking and low levels of healthy eating. Deaths from smoking, heart disease, stroke and cancer are also worse than the national average. Alcohol related hospital stays and drug misuse are also worse than national comparators. Diabetes prevalence is at the national level\textsuperscript{226}. 
7.4 The Type 1 Diabetes Outpatient Clinic

A diabetes clinic has been operating at the Walton Hospital site (now part of University Hospitals Aintree NHS Foundation Trust) since the 1950s. Previously this operated in the form of a large outpatient clinic (100 patients) once a week; with other smaller clinic sessions for new patients, urgent referrals, young adults and pregnant patients. A review of the service was carried out in 1987. At that time the diabetes service was staffed by two Consultant Physicians with an interest in diabetes, one senior registrar and two registrars. Occasional help was provided by a senior house officer. Two diabetes specialist nurses worked full-time and there was help on a sessional basis from district dieticians and the hospital chiropodist. There were around 6000 attendances at the clinic annually by about 2400 patients.

At the service review the future needs of the diabetes service were assessed and the possibility of a separate diabetes centre proposed. This resulted in an increase in staff, such that new posts were created and filled and a new diabetes centre to house the diabetes service and specifically the diabetes clinics agreed\textsuperscript{227}. The building was completed in the spring of 1990. It is shown below in 2009.

Fig 7.4.1 Walton Diabetes Centre Outpatient Clinic
The young adult diabetes clinic was set up in 1991. The clinic is contained within the purpose built diabetes centre, which allows for nurse assessment and recording of physical data. There are separate consultation rooms for patient contact with diabetes specialist nurses, doctors and dieticians.

The clinic has been run by the same consultant physician with specialist interest in Diabetes and Endocrinology since its inception. It has been supported by the same specialist nurse and has the services of a dietician. Initially the clinic took over the care of patients, from the main Children’s Hospital. These patients were resident in the catchment area and once they reached 16/17 yrs of age their care was moved to this adult service. These patients then continued in this clinic. Younger patients from the other clinics at this centre also had their care in this clinic, such as those newly diagnosed with diabetes whilst an adolescent or young adult.

The clinic was run with the aim of optimising diabetes care to enable good glycaemic control with freedom from troublesome hypoglycaemia. All patients were encouraged to choose a basal bolus regime of insulin administration, adopt healthy lifestyle choices and discouraged from smoking. As the targets for glycaemic control altered over the following decade and beyond, care was kept in line with the contemporary guidelines. Over latter years cardiovascular management was also a prominent aspect of the overall management as blood pressure, cholesterol and ACR were targeted.

Patients were given appointments as frequently as the system allowed (no less than yearly) and often attended 3-4 times per year. Clinic defaulters were offered further appointments, and chronic non-attendees were contacted at home by the specialist nurses, often resulting in a home visit. All patients were able to contact the specialist
nurses for advice by telephone and were often reviewed in a nurse run clinic if there were specific problems. The clinic continues to run with these guiding principles.
7.5 The younger adult patients with type 1 diabetes studied

Demographic and biophysical data had been recorded on the patients attending the younger adults T1DM clinic since it began. This data has been collated and forms the basis of the patient cohort which has been retrospectively reviewed at intervals over a 10-15 year time period.

Initially the data was examined to identify a group of patients who had been attending regularly over a minimum of 5 years. Those who met these criteria had their case notes reviewed in detail, allowing all available records of HbA1c, blood pressure, total cholesterol, urinary microalbumin/creatinine ratio, weight, BMI, insulin type and dosage and other medication to be recorded. Any specific complications attributable to diabetes were noted, as were other co-morbidities. This allowed an extensive database to be constructed.

Statistical average values were calculated for each variable over a minimum of five years between 1996 and 2001. Some patients had attended regularly for a greater time period and their values were averages of this greater time period. The mean values for the group as a whole were also calculated. Those patients who changed their care to another service, moved area, defaulted from the clinic or died were noted so as to allow comment on the shifting nature of the clinic population. Patients who first attended the clinic after the end of 1996 were not included in any analyses.

Subsequent to this, the same patients were reviewed in 2006 (all attendances) and the same variables collated. Thus an average for 2006 was generated for each patient and the group as a whole. Once again those patients who were no longer attending were identified and comment made. The dispersion of the original cohort by end of 2006 is detailed in Table 7.5.1.
Table 7.5.1

<table>
<thead>
<tr>
<th>Year</th>
<th>Number Attending</th>
<th>Default/Discharged</th>
<th>Moved</th>
<th>Dead</th>
<th>Clinic Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-1996*</td>
<td>386</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2001</td>
<td>261</td>
<td>92</td>
<td>11</td>
<td>22</td>
<td>-125</td>
</tr>
<tr>
<td>2006</td>
<td>214</td>
<td>34</td>
<td>8</td>
<td>5</td>
<td>-47</td>
</tr>
</tbody>
</table>

*Regular attendees at the Walton Diabetes Centre Outpatient Clinic 1991-1996, and subsequently followed in other years

It is worthwhile considering the potential similarities or differences between the patients who continue to attend and those eventually lost to the clinic. The glycaemic control of the different groups is shown in the table below (7.5.2). These are average HbA1c results for each group.

Table 7.5.2

<table>
<thead>
<tr>
<th>Group</th>
<th>Number in group (n)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Cohort 1991-1996</td>
<td>386</td>
<td>9.19</td>
</tr>
<tr>
<td>Interval ‘Loss’</td>
<td>125</td>
<td>9.32</td>
</tr>
<tr>
<td>Cohort 2001</td>
<td>261</td>
<td>9.10</td>
</tr>
<tr>
<td>Interval ‘Loss’</td>
<td>47</td>
<td>9.33</td>
</tr>
<tr>
<td>Cohort 2006</td>
<td>214</td>
<td>8.66</td>
</tr>
<tr>
<td>Total ‘lost patients’</td>
<td>169</td>
<td>9.32</td>
</tr>
</tbody>
</table>

Those patients who continue to attend the clinic demonstrate a lower HbA1c than those who defaulted, died or moved away (further review of these differences is made in the following chapter). This may reflect an underlying difference between
the two groups, which could somehow explain the differences in HbA1c. However it is possible, and also more likely that it shows that those with continued diabetes team input and clinic attendance have an improved HbA1c. Whether this is due to self-selection by these patients – those interested in self-care continue to attend- or that the input they receive when attending effects this improvement is not apparent, although both aspects probably contribute.

The final 214 patients who continued to attend in 2006 were not dissimilar to the whole cohort originally recruited in 1991-1996, except of course being older and having a longer duration of diabetes. Their average ages at diagnosis of diabetes (20.43 years (2006) v 19.08 years (original)) and the proportion of men within the groups were both similar (134 (62.6.%) 2006 v 233 (60.3%) original). It is reasonable then to suggest that the 214 patients still attending at the end of 2006 were representative of the original cohort of patients reviewed.
8.  Glycaemic control in a type 1 diabetes clinic for younger adults.

S.A. Saunders, M. Wallymhamed, I.A. Macfarlane.

QJM 2004;97:575-80
8.1 Introduction

The intensive therapy group of the Diabetes Control and Complications Trial (DCCT) demonstrated that tight glycaemic control (HbA1c <7%) in young adults with Type 1 diabetes reduced the incidence of microvascular disease, when compared to conventional care at that time. The beneficial effects of tight glycaemic control in the DCCT on microvascular complications were maintained in the long term, despite subsequent deterioration in HbA1c values. Since the publication of the DCCT, tight glycaemic control with HbA1c <7%, has been one of the central aims of diabetes care.

The intensive therapy arm of the DCCT was, however, expensive in terms of frequent clinic contact. Patients were reviewed on a monthly basis by a physician and had weekly contact with specialist nursing staff. Also, the rate of serious hypoglycaemia and the mean weight of patients in the ‘intensive therapy’ arm increased, something not seen in the ‘conventional therapy’ arm.

In 1991 a clinic for young adults with type 1 diabetes was established at our hospital. Since then it has been staffed by the same specialist diabetes physician and diabetes specialist nurse with a dietician also present. Throughout, the main aims of the clinic have been optimal glycaemic control without troublesome hypoglycaemia and screening for diabetic complications. This study reports the glycaemic control achieved in this clinic and searched for factors associated with poor control.
8.2 Patients and Methods

The young adult type 1 diabetes clinic was based in University Hospital Aintree, Liverpool, North-West England. The patients lived mainly in an urban area and originated from a wide spectrum of social groups.

The same diabetes specialist physician and diabetes specialist nurse have staffed the clinic during the study period. All patients saw the clinic dietician at least once and the great majority had multiple dietetic reviews. Follow up appointments were offered at least twice yearly, the more problematic patients receiving more frequent follow-up appointments. Non-attendees were sent further appointments (at least 3) and finally a home visit by the specialist nurse to encourage re-attendance and to maintain care was made.

There were 386 Type 1 patients who attended the diabetes clinic in the 6 years between 1991 and 1996 and who had more than one recorded attendance. Data was obtained and reviewed from the case-notes of the clinic visits of these patients up until December 2001. At each attendance, HbA1c (DCCT aligned) was measured and total mean values throughout the study for HbA1c were calculated. The insulin dose units/kg body weight was recorded at last attendance and compared with data from the end of the DCCT\textsuperscript{150,228}. Attendance rates at diabetes outpatient appointments were calculated (attended/total appointments offered), and hospital admissions for ketoacidosis and hypoglycaemia recorded. Admitted smoking habit at enrolment was noted and known deaths were also recorded.
8.3 Statistical Analyses.

The individual patient data is not available for the DCCT patients. However, chi
squared test were used to compare prevalence data from the DCCT and Aintree
patient groups. The mean values for each patient were combined to allow the
calculation of total means, for the whole cohort. This was done for each variable.
Data from the Aintree cohort is expressed as mean (±standard deviation).
Comparison between groups within the Aintree cohort is made by the Mann-Whitney
U-test, correlation was assessed by Pearson’s correlation coefficient, significance
taken as p <0.05.
8.4 Results.

8.4.1 Demographic data (Table 8.4.1)

The demographic data from the Aintree cohort are shown compared to those of the DCCT cohort. The Aintree cohort contained more male patients (60%) compared to the whole DCCT cohort (53%) \((p = 0.015\) chi squared). The age at first attendance of the Aintree clinic patients was similar to the age at which patients were recruited to the DCCT (mean age \((±SD)\) Aintree 29±10 vs DCCT 27±7). However, the duration of diabetes in the Aintree cohort at recruitment was considerably greater: (9.5yrs Aintree vs 2.6yrs (DCCT primary prevention) vs 8.8yrs (DCCT secondary prevention). The patients in the primary prevention group of the DCCT were chosen specifically because they did not demonstrate any diabetic retinopathy and had duration of diabetes between 1 and 5 years. It is clear therefore that the Aintree group were closer to the patients in the secondary prevention arm of the DCCT with regard to duration of diabetes.

8.4.2 Attendance and Follow-up (Table 8.4.2)

386 patients attended the Aintree clinic between 1991 and 1996 that had more than one recorded attendance. At end of 2001, in the previous 2 years 261(67.6%) had attended at least once, 92(23.8%) had defaulted persistently, 11(2.8%) were known to have moved away and 22(5.8%) had died. There had been a total of 4014 attendances during the study.

The Aintree cohort had a mean follow-up period longer than the patients in the DCCT (7.7 vs 6.5yrs). In the DCCT 99% of patients completed the study and attended 95% of their hospital appointments, in contrast, 23.8% of the Aintree cohort had persistently failed to attend reviews in the last 2 years. Only 11 (0.7%) of the DCCT group died during the study period, compared to 22 (5.8%) of the Aintree
The Aintree patients who died had significantly longer duration of diabetes and were older at diagnosis of diabetes compared to those who continued to attend the clinic and those who failed to attend in the past 2 years. The total mean HbA1c levels between these groups did not differ. (Table 8.4.2).

The clinic non-attendance rate (defined as the ratio of appointments not attended to the total number of appointments offered during the study) was 0.32. There was a significant correlation between the non-attendance rate and higher mean HbA1c levels ($r = 0.14$, two tailed $p=0.029$).

### 8.4.3 Glycaemic control

The mean of all the HbA1c measurements over the study period from the 386 Aintree patients was 9.19%. This was very similar to the conventionally treated cohort of the DCCT (mean HbA1c 9.1%). Only 3.6% (14 patients) of the Aintree cohort achieved a total mean HbA1c <7% during the study. In comparison the DCCT intensive therapy arm achieved a total mean HbA1c of 7.4% throughout the study.

### 8.4.4 Insulin administration and dosage

At the last recorded clinic attendance the majority (58%) of the Aintree cohort were administering insulin by multiple daily injections (MDI-short acting insulin, human or analogue, with meals, three times a day and isophane insulin at bedtime.) There was no significant difference in total mean HbA1c (%) between those patients administering insulin by MDI compared with those who elected to continue using human soluble and isophane insulin mixtures twice daily ($9.1 \pm 1.2$ vs $9.2 \pm 1.3$;
p<0.6). The mean amount of insulin (U/kg/day) at last recorded visit was not significantly different (0.75±0.2 MDI vs 0.67±0.17 twice daily insulin; p<0.8). In the Aintree patients the mean prescribed dose to all patients, of insulin per kilogram body weight at the last recorded patient visit was similar to that at the end of the DCCT; mean 0.74 units/kg/day (n=386, Aintree 2001), vs 0.75 units/kg/day in the (Former DCCT intensive therapy group n= 687) and vs 0.67 units/kg/day (Former DCCT conventional therapy group, n=688, data from EDIC enrolment\textsuperscript{228}).

8.4.5 Hypoglycaemia
Severe hypoglycaemia, (requiring hospital admission) occurred in 0.79 per 100 patient years of follow-up in the Aintree patients, similar to the conventional therapy arm of the DCCT (0.77 per 100 patient years). The intensive therapy arm of the DCCT had a higher rate of admission, 1.14 per 100 patient-years (p<0.001 vs conventional therapy DCCT). Those Aintree patients who had severe hypoglycaemia (n=18) had similar total mean HbA1c levels compared to the 368 patients who did not (9.3±1.4 vs 9.1±1.3; p=0.5).

8.4.6 Diabetic Ketoacidosis (DKA)
In the Aintree cohort the DKA rate was 2.39 episodes per 100 patient-years. This was higher than in the DCCT; 1.8 and 2.0 episodes per 100 patient-years in the conventional and intensive therapy groups respectively. The 39 patients from the Aintree cohort who had least one admission with DKA had a significantly higher total mean HbA1c in comparison to the 347 patients without such an admission (10.1±1.1 vs 9.0±1.3; p<0.0001).
The patients allocated to the primary prevention arm of the DCCT had no retinopathy changes at baseline, whilst those in the secondary prevention arm had retinopathy (greater than background) in around 40% of the patients. This microvascular complication is the one most commonly recorded (presence or absence, background, laser treated or blindness) in the Aintree clinic population, although this data was not available for when they first attended the clinic, data was recorded by review in 2001.

The data showing the prevalence of retinopathy at review in 2001, as well as other relevant details are shown in the table 8.4.3. In essence, the patients without documented retinopathy in 2001 (141pts (37.9%)) had a lower mean HbA1c (8.86% v 9.32%) and shorter duration of diabetes (15.49yrs v 21.84 yrs) than those with retinopathy (231pts (62.1%). Direct comparison with the patients in the DCCT is not possible, due to the way data was recorded for retinopathy in that trial, and the lack of comparable data in the Aintree patients. What is similar however is that those patients with shorter duration of diabetes and a lower HbA1c demonstrate a lower prevalence of retinopathy than the comparator group. This mimics the contrast between the intensive v conventional control arms in the DCCT. The graphs below show the prevalence of complications in the Aintree cohort with reference to the duration of diabetes (graph 8.4.1). Secondly, a comparison is made between the prevalence of complications in those patients in the DCCT primary prevention arm and those patients in the Aintree cohort of similar duration of diabetes (graph 8.4.2). The same details are shown for the secondary intervention arm also (graph 8.4.3).
8.5 Discussion

The reductions in HbA1c levels achieved in the intensive therapy arm of the DCCT was associated with decreased rates in the appearance and progression of microvascular complications in comparison to conventional therapy at that time. These differences in complications persisted even though the differences in glycaemic control between the two therapy arms narrowed after the trial ended\textsuperscript{147}. The benefits of tight glycaemic control in preventing or delaying microvascular complications are therefore clear. However can tight glycaemic control be achieved in routine clinical practice?

Our study directly compares the results from a young-adult type 1 diabetes clinic with the results achieved in the DCCT. The Aintree clinic, had from the outset, the aims of tight glycaemic control, i.e. the lowest HbA1c level possible, by encouragement of multiple daily insulin injections (four times daily) and they were reviewed by the same specialist doctor and nurse with dietician input. Freedom from troublesome hypoglycaemia however, was also a major aim. The results show that, over a longer follow-up period than reported in the DCCT, glycaemic control was not as tight as the DCCT intensive therapy arm and was similar to the DCCT conventional therapy arm. It is likely that the explanation for this is multifactorial. The Aintree patients had longer duration of diabetes and unlike the DCCT patients, were not a selected group of highly motivated subjects who had enrolled in a trial. The socio-economic status of the two groups will no doubt have differed, although the Aintree patients did not have documented social status, it may be inferred from the prevalence of smokers within the group. The DCCT patients were, in contrast, predominantly white middle-class people who were motivated enough to volunteer for a clinical trial. They also failed to attend one third of their clinic appointments and the non-attendance rate was associated with higher HbA1c levels. There was a loss of one third of the clinic population over the 11 years studied, from patients
moving away, persistently failing to attend or dying. Failure to attend UK diabetes clinics by 20-30% of patients have been documented previously 161, 163, 229. The total mean HbA1c of the persistent two-year non-attendees, was found to be similar to the total mean HbA1c of the patients who continued to attend the clinic. It is likely that many of these long-term defaulters had, in fact, moved away and failed to inform the clinic.

Compliance with insulin dosage is another factor influencing HbA1c levels. Although the recorded prescribed dose of insulin in the Aintree patients was similar to that given in the DCCT groups, it is likely that some Aintree patients did not comply. Evidence from Scotland, suggests that up to 28% of young patients may not use insulin at the prescribed doses, leading to persistent under-use of insulin and chronically poor control160.

The avoidance of serious hypoglycaemia was an important part of the management of the Aintree patients and hospital admissions with hypoglycaemia were fewer than in the intensive therapy group of the DCCT. Undoubtedly many Aintree patients would have reduced their insulin dose when hypoglycaemic episodes occurred, resulting in higher HbA1c levels in some patients151.

Omission of insulin by patients, for whatever reason, places them at risk of diabetic ketoacidosis (DKA). There was no apparent difference in the rates of admission to hospital as a result of DKA between the Aintree cohort and the DCCT patients, and no differences between the DCCT therapy arms. However, the Aintree patients who were admitted with DKA had a significantly higher HbA1c than those not admitted.

None of the Aintree patients were treated with continuous subcutaneous insulin infusions (CSII) in contrast to many patients in the intensive cohort of the DCCT. Some studies suggest that use of CSII may confer an advantage over MDI in achieving better glycaemic control43, 230. However there are obvious limitations of
small studies using selected volunteer patients. Also, other studies have suggested there is no advantage to be gained in terms of glycaemic control by using CSII\textsuperscript{231, 232}. CSII is more expensive than MDI administration, requires a highly motivated patient without psychological problems, and an experienced diabetes team who can provide regular and frequent input into the ongoing care of the patient\textsuperscript{42}.

Recently, further strategies have been introduced to optimise glycaemic control. These include an intensive education programme; Dose Adjustment for Normal Eating (DAFNE)\textsuperscript{192}, and newer analogue insulins\textsuperscript{110, 172, 183, 184, 233-235}. DAFNE may produce short-term improvements in HbA1c levels but long-term data on sustained tight control is lacking. Again, a highly motivated patient willing to commit time and comply with advice is needed, along with considerable nurse educator resources.

The recently introduced long-acting analogue insulin Glargine may be useful in improving fasting hyperglycaemia and reduce the incidence of hypoglycaemic episodes in patients with type 1 diabetes\textsuperscript{181, 183, 233, 234, 236}. It is possible the use of long acting analogues may encourage the patient to aim for tighter glycaemic control without the fear of hypoglycaemia leading to defensive reductions in insulin doses.

Is the goal of tight glycaemic control, achievable in unselected Type 1 clinic patients? The results from the Aintree cohort suggest that the great majority of patients will not achieve this, although long-acting analogue insulin and CSII were not used. Many barriers to tight glycaemic control exist in the ‘real-world’ that are not found in clinical trial settings. Many patients do not comply with regimens long-term, commonly fail to attend clinic regularly or move away from the clinic area. Appointments cannot be offered as frequently as visits in clinical trials due to resource limitations. Despite the somewhat disappointing HbA1c levels achieved in this large cohort of young patients, well organised, structured diabetes clinics have a
very important role to play in the screening and early treatment of microvascular complications.
Table 8.4.1. Demographic data from the Aintree clinic and DCCT cohorts of Patients with Type 1 diabetes at enrolment.

<table>
<thead>
<tr>
<th>Aintree Patients</th>
<th>DCCT Patients</th>
<th>1° Prevention</th>
<th>2° Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conventional</td>
<td>Intensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conventional</td>
<td>Intensive</td>
</tr>
<tr>
<td>N (% male)</td>
<td>386(60)</td>
<td>378(54)</td>
<td>348(49)</td>
</tr>
<tr>
<td>Mean (SD) Age (yr) at enrolment</td>
<td>29± 10</td>
<td>26± 8</td>
<td>27± 7</td>
</tr>
<tr>
<td>Mean (SD) Duration of T1DM at enrolment</td>
<td>9.5± 8.1</td>
<td>2.6±1.4</td>
<td>2.6± 1.4</td>
</tr>
<tr>
<td>% Smokers</td>
<td>31</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>
Table 8.4.2. Glycaemic control (HbA1c) data from the Aintree Clinic Cohort up to December 2001 (Mean follow up 7.7±3.01 yrs after enrolment)

<table>
<thead>
<tr>
<th>Aintree Clinic</th>
<th>Number of Patients (% Total)</th>
<th>Mean Age at diagnosis of diabetes Yrs. (±SD)</th>
<th>Duration of Diabetes Yrs at enrolment. (±SD)</th>
<th>Mean HbA1c % (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attended in last 2 years</td>
<td>261 (67.6)</td>
<td>18.6 (9.0)</td>
<td>8.5 (7.1)</td>
<td>9.1 (1.3)</td>
</tr>
<tr>
<td>Persistent defaulters in last 2 years</td>
<td>92 (23.8)</td>
<td>19.6 (10.7)</td>
<td>10.4 (8.8)</td>
<td>9.2 (1.5)</td>
</tr>
<tr>
<td>Known moved Away</td>
<td>11 (2.8)</td>
<td>14.3 (7.6)</td>
<td>9.9 (9.7)</td>
<td>9.3 (1.5)</td>
</tr>
<tr>
<td>Dead</td>
<td>22 (5.8)</td>
<td>25.0 (11.8)</td>
<td>16.7 (9.6)</td>
<td>9.5 (1.5)</td>
</tr>
</tbody>
</table>

* – p<0.0001 vs patients still attending, and persistent defaulters
Table 8.4.3 Detailing the prevalence of retinopathy in the Aintree patients in 2001.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aintree Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retinopathy</td>
</tr>
<tr>
<td>Number (%)</td>
<td>240 (62.1%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.32</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>21.84</td>
</tr>
<tr>
<td>Ex smoker</td>
<td>22 (9.16%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>65 (27.08 %)</td>
</tr>
</tbody>
</table>
Graph 8.4.1  Shows the prevalence of documented microvascular complications in the Aintree cohort at last clinic attendance 2001.
Graph 8.4.2 Shows the prevalence of complications in the Aintree cohort with duration of diabetes (10-15 years) in comparison to the Primary prevention arm of the DCCT at completion (11.5 years average duration of diabetes).
Graph 8.4.3 Shows the prevalence of complications in the Aintree cohort with duration of diabetes (16-20 years) in comparison to the Secondary intervention arm of the DCCT at completion (18.5 years average duration of diabetes).
9. Improvements in glycaemic control and cardiovascular risk factors in a cohort of patients with type 1 diabetes over a 5-year period.

S.A. Saunders, M. Wallymhaled, I.A. Macfarlane.

QJM 2009;102:29-34.
9.1 Introduction.

The care of patients with diabetes has changed considerably in the past decade. Developments in insulin technology have lead to the increased use of analogue insulin, particularly in patients with Type 1 Diabetes (T1DM). Indeed, the delivery of insulin has also changed with the development of pen\textsuperscript{38, 40}, and more recently inhaled devices- although this has been with varying degrees of success\textsuperscript{47, 48}. There has also been change in diabetes education programmes and the integration of this with adjustment of both diet and insulin dose\textsuperscript{192}. The use of insulin pumps has increased, although in the UK this increase has not been as rapid or large as some would hope\textsuperscript{42}.

In tandem with a more patient centred approach, such changes would hope to improve the quality of life of patients as well as decrease the risk of complications of diabetes by improving glycaemic control. This had been the aim of diabetes services since before the publication of the landmark Diabetes Control and Complications Trial\textsuperscript{1} however its’ findings demonstrated this and served to focus services on the importance of glycaemic control in the prevention of complications of diabetes.

Furthermore, other modifiable cardiovascular risk factors, such as serum cholesterol and blood pressure have come under increased scrutiny and led to a series of guidelines being published by prominent bodies. This has resulted in ‘target’ values being recommended; these targets have become increasingly tight over the last few years as evidence accumulates of the benefits of risk factor control.

In the UK, the publication of the National Service Framework for Diabetes in 2001\textsuperscript{130} was both an attempt to standardise diabetes care nationally and ensure its uniform delivery. The recommendations applied to both Primary and Secondary care.

This was followed, more recently, by the developments that have occurred in Primary care as a result of the Quality Outcomes Framework (QoF) being instituted
in 2005\textsuperscript{237}. This has been followed by a shift in general health policy with the drive towards chronic disease management, including diabetes, being predominantly led by community and primary care services where appropriate.

We therefore felt it was appropriate to assess what effect, if any, such changes have had on the care of a cohort of patients with T1DM who have been attending the same Diabetes outpatient clinic since \textit{before} and \textit{through} many of these developments.
9.2 Methods.

We had previously assessed a cohort of patients in 2001, who had been attending the same diabetes outpatient clinic at an urban hospital in Liverpool, in the North-West of England. These patients were all known to have Type 1 Diabetes (T1DM). They originally began attending the young-adult clinic between 1991 and 1996, and during that time had at least two consecutive attendances. They were seen by the same Consultant Physician and Diabetes Nurse Specialist. During that time they had been managed under the principles of tight glycaemic control but with freedom from recurrent hypoglycaemic events. The patients were also encouraged to use a flexible insulin regimen in the form of three short-acting and one long-acting insulin injection (MDI / Basal-Bolus). The choice to do this, or remain with twice daily premixed insulin injections, ultimately remained with the patient. They were all seen by a dietician at least once. Other healthy lifestyle choices e.g. smoking cessation and regular exercise were also reinforced. Management of blood pressure, cholesterol and screening and treatment of microalbuminuria was in line with contemporary guidelines.

Due to the evolving nature of diabetes care, the progression in technology and the increasingly pro-active treatment of cardiovascular risk factors, we decided to review the remaining patients who were attending the same clinic in 2006; assessing what change, if any, had occurred in biophysical markers, medications and outcome in the intervening five years.

Originally, in 2001 all previous clinic attendances of all eligible patients were reviewed. Biophysical data from each attendance was recorded. Average values for each variable of each patient were calculated during their period of follow-up. Data for the whole patient group was then presented as an average of these values. In early 2007, a review of the clinic attendances during the year ending December 31st 2006 was performed. Data from the last outpatient clinic attendance during 2006
was recorded. Once again, average values were calculated, allowing this data to be compared with the average data obtained previously. Current medication use was recorded; this was compared to the recorded medication from their last attendance in the previous review. Patients who were no longer attending the clinic, but who had been included in the earlier assessment were not reviewed here, although record was made of these patients.
9.3 Statistical analyses.

All data was assessed for normality of distribution. Parametric data was analysed using students’ t-test (matched or non-matched) where appropriate. Non-parametric data analysis was made using Mann-Whitney U Test. Comparison of use of medication was calculated using the test of significance on two independent proportions. Significance was taken to be a p value of <0.05. All data analysed using StatsDirect version 2.6.5., StatsDirect, Cheshire, WA14 4QA, UK.
9.4 Results.

Between 1991 and 1996 three hundred and eighty-six patients attended at least once and had recorded biophysical data. The full details of the cohort are detailed in the table below. There were 214 patients of the original cohort still attending the clinic by the end of December 2006. These patients had an average duration of diabetes of 23.46 (SD± 8.06) years. There were 134 male patients (62.62%).

<table>
<thead>
<tr>
<th>Year</th>
<th>Number Attending</th>
<th>Default/Discharged</th>
<th>Moved</th>
<th>Dead</th>
<th>Clinic Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-1996*</td>
<td>386</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2001</td>
<td>261</td>
<td>92</td>
<td>11</td>
<td>22</td>
<td>-125</td>
</tr>
<tr>
<td>2006</td>
<td>214</td>
<td>34</td>
<td>8</td>
<td>5</td>
<td>-47</td>
</tr>
</tbody>
</table>

Table 9.4.1

9.4.1 Non-Attendees

Of those that were no longer under the review of the clinic, five had died, their average age at death being 58.8 (SD± 12.78) yrs, and duration of diabetes 40.6 (SD ±7.64) yrs. Thirty-four patients had either been discharged due to persistent non-attendance (28 pts) or had had their care transferred to another diabetes clinic or consultant (6 pts). A further eight patients were lost to follow-up by the clinic. The HbA1c of this group at last recorded attendance was 9.33% ±1.4 (not significantly different from the 214 continued attendees, by Mann Whitney U Test p=0.21).

9.4.2 Continued Attendees

The exact data on the patients in 2001 has been published elsewhere. The 214 patients seen and reviewed in the year 2006 had an average age of 43.66 (SD 9.59)
yrs and an average duration of diabetes of 23.45 (SD 8.06) yrs. The data obtained in 2001 was then compared with the most recent data to see if any significant changes had occurred in the intervening years. Table 9.4.2 shows the baseline data from both interval analyses and the statistical significance of any differences. The change in the values is also shown, expressed as a value relative to the 2001 data and demonstrates that small changes have occurred during the intervening period in these patients. The most apparent change occurring in the mean total cholesterol values. Interestingly, both weight and BMI have seen small relative increases in the same time period, whereas the total insulin dose does not appear to have increased by the same proportion.

The results also show that in the intervening period these 214 patients have seen a significant reduction in their mean HbA1c, diastolic blood pressure, urinary ACR and total cholesterol. There was however a significant increase in their weight and body mass index over the same period. No significant change could be found in plasma creatinine levels or systolic blood pressure. There was no significant change in the units of insulin used per kilogram of body weight during this time.

9.4.3 Guidelines

During the period preceding the 2001 data collection, the guidelines for management of patients with T1DM in our clinic were roughly based around the results of the DCCT study; that is to say, we strived for tight glycaemic control with the a target value of less <1% higher than the normal range. Blood pressure management was aimed at the then recommended guidelines of the recently published Joint British Societies Guidelines239, that is a systolic blood pressure of <130 mmHg and a diastolic blood pressure of <80 mmHg. Total cholesterol values were targeted at values of <5 mmol/l. Although no guidelines were published as
such, we aimed to maintain serum creatinine in the normal range, and as recommended screened annually for microalbuminuria (taken as >3.5 mg/mmol in the data used here). Both of these are clearly influenced by glycaemic control and the latter by blood pressure control.

Ideally we also tried to maintain a normal body weight and BMI by encouragement of a healthy diet and exercise.

The proportion of the clinic patients achieving many of the targets in 2001 was less than ideal (shown in table 9.4.3). Gratifyingly there was a high proportion of patients reaching the blood pressure targets, and the majority of our patients had normal mean ACR and mean creatinine. The use of the estimated glomerular filtration rate (eGFR) was not in common clinical practice at that time. The proportions of the cohort achieving the targets in 2006 are also shown. Comparison of the two groups demonstrates the differences in proportion achieving the relevant targets. Although the target for systolic blood pressure had become lower over the review period, nearly two thirds of the cohort was still in the recommended range. The recommendation for diastolic blood pressure had remained the same, and the proportion of the cohort achieving it had increased from 84.58% to 93.93%. Similarly, even though the glycaemic target had dropped from <7% to <6.5%, more patients in the cohort were within the target range. It is noteworthy that the number of patients a normal BMI had decreased over the intervening period for 107 to 63. A clear change in prescription of medication had also occurred in the five years between the two guidelines.

9.4.4 Medication

The use of medication to achieve these targets was also reviewed. The data gathered here was from the declared medication at the time of the patients' most
recent clinic visit up to Dec 31st 2001 and their declared medication at the last visit in 2006. The guidelines in 2001 were more cautious in the treatment of cardiovascular risk factors in patients with T1DM, than perhaps current ones are. Most of the patients were on a pre-mixed biphasic regime of insulin administration, the type of insulin used was not accurately recorded and consequently we were unable to determine whether the newer analogue insulins were being used to any degree. Only small proportions of the clinic population were being treated actively for raised blood pressure, cholesterol or nephropathy as determined by a raised ACR. This data is shown in table 9.4.4 below.

It is noticeable that an increase in the use of MDI insulin, ACE inhibitors/ARBs, Statins, other blood pressure medication and even Metformin (no patients were using metformin when assessed in 2001) had occurred over the review period.

Following the review of the data in 2001, diabetes management underwent change. The contemporary guidelines suggested more aggressive management of cardiovascular risk factors, even the management of hyperlipidaemia in patients with T1DM was subject to a more aggressive approach, despite the wealth of evidence on this subject being for patients with type 2 diabetes. The most recent; that is up until the end of 2006, guidelines from the American Diabetes Association, and the Joint British Societies are given in table 9.4.5.

It is possible to estimate the overall improvement in cardiac risk of these patients using a cardiovascular risk calculator. If we treat the average values of the two groups, as detailed in table 9.4.2, as the risk factors then any potential improvement can be gauged. In this instance the risk calculator based upon the JBS2 guidance is used (http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp).

For the patient group reviewed in 2001 the following factors were used:
(Age- 44, Sex- male, Diabetes-yes, Systolic BP-126, Total Cholesterol-5.37) --
Probability of dying from cardiovascular disease in next 10 years is 1.1 
Assumption made that HDL=1.0.

Whilst in the group reviewed in 2007:

( Age-44, Sex-male, Diabetes-yes, Systolic BP-126, Total cholesterol- 4.62) --
Probability of dying from cardiovascular disease in next 10 years is 0.8%.
Assumption made that HDL=1.0.

Age was left the same in both groups to negate natural aging and smoking status was assumed to be non-smoker as only 30% of the groups were current smokers.

This shows that even the marginal differences between the two analyses can contribute to a reduction in overall cardiovascular risk.

As illustrated previously in Table 9.4.3, blood pressure targets were tighter than in 2001, with a systolic target of less than 130 mmHg. Glycaemic targets were also tighter, aiming at levels less than 6.5%. Cholesterol targets were also lower with an optimal value of < 4.0 mmol/l.

The results show that in a group of patients followed up in the same clinic for an extended period of time by the same diabetes team, small but statistically significant improvements in the biophysical measurements of disease can be made. These changes may well reflect a changing approach in the management of the risk factors for glycaemic control and cardiovascular disease over more recent years and result in reduction in the of risk of future cardiovascular events.
Table 9.4.2  All numbers are mean values for the cohort (n=214) in the years when reviewed.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patient cohort 2001</th>
<th>Patient cohort 2007</th>
<th>Relative % Change since 2001</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9.06 (± 14.35)</td>
<td>8.66 (± 1.43)</td>
<td>-4.41</td>
<td>P = 0.0002 *</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>126.43 (± 6.56)</td>
<td>126.13 (± 18.97)</td>
<td>-0.24</td>
<td>P = 0.8148</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>73.55 (± 15.25)</td>
<td>67.38 (± 9.73)</td>
<td>-8.39</td>
<td>P &lt; 0.0001 *</td>
</tr>
<tr>
<td>Microalbumin / Creatinine ratio</td>
<td>5.82 (±21.84)</td>
<td>5.49 (± 16.26)</td>
<td>-5.67</td>
<td>P = 0.0033 *</td>
</tr>
<tr>
<td>Creatinine</td>
<td>93.70 (± 0.97)</td>
<td>96.24 (± 46.20)</td>
<td>2.71</td>
<td>P = 0.0909</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>5.37 (± 11.75)</td>
<td>4.62 (± 0.90)</td>
<td>-13.97</td>
<td>P &lt; 0.0001 *</td>
</tr>
<tr>
<td>Weight</td>
<td>75.04 (± 3.41)</td>
<td>82.31 (± 14.79)</td>
<td>9.69</td>
<td>P &lt; 0.0001 *</td>
</tr>
<tr>
<td>BMI</td>
<td>25.32 (± 0.27)</td>
<td>27.72 (± 5.17)</td>
<td>9.49</td>
<td>P &lt; 0.0001 *</td>
</tr>
<tr>
<td>Insulin Units / Kg</td>
<td>0.75 (± 0.23)</td>
<td>0.79 (± 0.28)</td>
<td>5.33</td>
<td>P = 0.597</td>
</tr>
</tbody>
</table>
Table 9.4.3 * Significance taken as p <0.05. Values calculated by Mann-Whitney U test.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>2001 Target Value</th>
<th>Percentage of clinic at target in 2001 (number of pts)</th>
<th>2005 Target Value</th>
<th>Percentage of clinic at target in 2006 (number of pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt; 7%</td>
<td>3.74 % (8)</td>
<td>&lt; 6.5%</td>
<td>5.14% (11)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>&lt; 140</td>
<td>69.16 % (148)</td>
<td>&lt; 130</td>
<td>62.62% (134)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>&lt; 80</td>
<td>84.58 % (181)</td>
<td>&lt; 80</td>
<td>93.93% (201)</td>
</tr>
<tr>
<td>Microalbumin /Creatinine ratio mg/mmol</td>
<td>&lt;3.5</td>
<td>77.10 % (165)</td>
<td>&lt;3.5</td>
<td>83.64% (179)</td>
</tr>
<tr>
<td>Creatinine µmol/l</td>
<td>&lt; 120</td>
<td>95.79 % (205)</td>
<td>&lt; 120</td>
<td>93.93% (201)</td>
</tr>
<tr>
<td>Total Cholesterol mmol/l</td>
<td>&lt; 5.0</td>
<td>37.38% (80)</td>
<td>&lt; 4.0</td>
<td>27.10% (58)</td>
</tr>
<tr>
<td>Weight</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>BMI Kg/m2</td>
<td>20-25</td>
<td>50.00% (107)</td>
<td>20-25</td>
<td>29.44% (63)</td>
</tr>
<tr>
<td>Insulin Units / Kg</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 9.4.4 Values of significance compared using test of significance on two independent proportions.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percent and (Number) of clinic patients in 2001 using medication</th>
<th>Percent and (Number) of clinic patients in 2006 using medication</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice daily</td>
<td>62.61 % (134)</td>
<td>33.17 % (71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basal Bolus</td>
<td>33.18 % (71)</td>
<td>65.42 % (140)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>4.21 % (9)</td>
<td>1.40 % (3)</td>
<td>0.08</td>
</tr>
<tr>
<td>ACE inhibitor/ ARB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>26.16 % (56)</td>
<td>45.34 % (97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other Blood Pressure treatment</td>
<td>7.47 % (16)</td>
<td>22.43 % (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metformin</td>
<td>0%</td>
<td>15.89% (34)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 9.4.5 Comparison of ADA and JBS2 targets.

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>ADA targets 2005</th>
<th>JBS 2 Targets 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt;7.0 %</td>
<td>&lt;6.5 %</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>&lt;130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt;4.1 mmol/l</td>
<td>&lt;4.0 mmol/l</td>
</tr>
<tr>
<td>LDL- Cholesterol</td>
<td>&lt;2.6 mmol/l</td>
<td>&lt;2.0 mmol/l</td>
</tr>
</tbody>
</table>
9.5 Discussion.

Since the publication of the Diabetes Control and Complications Trial (DCCT) results healthcare professionals have strived, supported by good evidence, to improve the glycaemic control of patients with T1DM. This process has not always been easy, as many factors other than insulin use can influence the ability of the patient and the diabetes team to attain the recommended goals.\textsuperscript{160-163, 240, 241}

Perhaps, as a consequence of this, as well as the holistic nature of diabetes care teams, recognition of other influential cardiovascular risk factors in the morbidity and mortality of patients with T1DM occurred early and was reflected in the management guidelines produced by leading professional bodies. In more recent years, an early intervention and aggressive management policy has been advocated in guidelines with the overall aim of reducing the complications of diabetes.

Much as with the DCCT, it is important to assess if such aggressive recommendations are actually attainable in day to day clinical practice. Certainly, evidence demonstrates that sub selecting ‘at-risk’ groups within a clinic population, and intervening with focused and repeated targeting of the problem areas can improve outcomes in the short term, albeit in patients with type 2 diabetes.\textsuperscript{242, 243} One might expect a comparable approach to be similarly effective in patients with T1DM.

As effective as short term interventions may be, a sustained improvement in the risk factors is the ultimate goal; only by achieving these can improvements in morbidity and mortality hope to be effected. Our observations of a cohort of patients with T1DM, managed in the ‘real-world’ to contemporary standards, show that over a five year period small but statistically significant improvements in the biophysical markers can be made. It is clear, however that these improvements are small, and come at no little cost; the relative amounts of medication used by the patients...
increased significantly over the time period observed. If these improvements can be sustained and built upon, then the benefits to the patients in terms of improved health will be worth this aggressive approach.

When outcomes improve, it is important to ask which intervention was responsible; the difficulty in this situation is identifying the particular intervention which resulted in benefit. For example, glycaemic control is about far more than prescribing insulin. Issuing a prescription for insulin is only the first step; it is clear that education of the patient, and indeed continued communication between healthcare professional and patient, is as important. The DARTS-MEMO study\textsuperscript{160} clearly demonstrated that prescriptions for insulin, for patients with T1DM, were not always completed as expected. It was suggested that up to 28\% of the patients in this group had occasions of omission of insulin. If there was a singular reason for such omission then it may be easy to address but this is not the case.

Our cohort demonstrated significant changes in their insulin use. A shift from the predominant use of biphasic pre-mixed insulin to a multiple dose injection regime was one of the more obvious changes that had occurred. This clinic does not and never has offered an insulin pump service. Could a simple change of insulin regime be responsible for the improvement seen in glycaemic control? It is unlikely that this could be wholly responsible, although some improvements in control have been reported\textsuperscript{244}, other evidence would suggest no significant change\textsuperscript{245} occurs. The change to MDI in itself is not a clear matter because of the increased use analogue insulin, particularly with the multiple dose injection regimes. Less hypoglycaemia is reported to be experienced with analogue insulin use and the subsequent reduction in fear of hypoglycaemia could then allow a more aggressive dose titration policy and subsequent improvement in glycaemic control\textsuperscript{108, 172, 175, 246, 247} although not all evidence supports this\textsuperscript{248}. We feel that although improvements may be seen with changes to both multiple dose injections and analogue insulin and that this has
contributed to improved outcomes it is probably clinically more relevant to have regular useful contact with the patients and address any ongoing issues with self management to sustain any transient benefits.

What then of improvements in the other biophysical markers of disease such as blood pressure and cholesterol measurements? We followed contemporary guidelines and managed cholesterol and blood pressure accordingly. It can be seen from our results that there were small, but significant improvements in both of these parameters, although there was no significant improvement in systolic blood pressure. The reason for the fall in diastolic pressure but not systolic pressure isn’t clear, but it is a well recognised phenomenon\textsuperscript{249}. The benefits of risk reduction, although not well demonstrated when lowering diastolic pressure alone, when compared to lowering both systolic and diastolic parameters, does remain\textsuperscript{250}.

The results also show a significant fall in the total cholesterol over the two sample periods. There was no change in the dietary advice issued to these patients during this time. The approach of using statin therapy in this population is effective at lowering cholesterol, if a little controversial, with the suggestion that only those with overt nephropathy actually benefit from long term risk reduction\textsuperscript{251, 252}. In our group there was maintenance of mean serum creatinine values and no deterioration in the mean urinary microalbumin values, which may actually reflect good blood pressure control, given the known associations\textsuperscript{27, 28}. Aside from this, improvement in serum lipid profiles is also seen with improving glycaemic control.

That said, even on the rather crude analyses used to estimate risk in this paper, it is possible to demonstrate an improvement in cardiovascular risk in the group. This is of course more relevant in the light of the findings from the EDIC follow-up group on cardiovascular risk\textsuperscript{36} and further meta-analysis\textsuperscript{253}. Of course, the cardiovascular-risk score only details the presence or absence of diabetes and does not relate it to a
value of HbA1c. The findings from the EDIC follow-up paper would suggest that intensive glycaemic control is also protective against cardiovascular events when compared to conventional glycaemic control such that, intensive treatment reduced the risk of any cardiovascular disease event by 42 percent and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57 percent. The decrease in glycosylated haemoglobin values during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease.

What is clear however is the significant increase in the amount of medication required by the patients to achieve both blood pressure and cholesterol control. In the intervening period the use of medication to control both blood pressure and cholesterol increased dramatically. The pill-burden of patients with type 2 diabetes (T2DM) has been recognised for some time and is partially a factor in non-concordance with medication use. Patients with T1DM may now also be facing a similar problem as the use of medication to control cardiovascular risk factors increases in this group.

What also of the influence of guidelines for care which have changed over the period reviewed here? It is difficult to attribute overall improvements in care to a change in practice recommendations. The compliance with guidelines in a clinic setting is yet another variable and targets are individualised for each patient. On reviewing our data improvements may be seen in the proportion of patients achieving these goals, although less achieve the tighter targets set more recently, the proportion achieving the preceding goal have increased significantly. This would suggest that an overall drive to attain newer targets has had an effect on general care. Further improvements may be seen in the current group should we re-examine them in three to five years time.
The recent change in approach to management of chronic disease in the community due to the implementation of the Quality outcomes Framework (QoF) in the UK has, along with the National Service Framework for Diabetes (NSF- Diabetes), served to bring uniformity to the delivery of diabetes care but whether the QoF system will lead to further gains in improving cardiovascular risk factors in patients with T1DM remains to be seen. It may be reasonable to suggest that the continuing care given by primary care physicians; the expert input which can only come from a specialist diabetes care team and continuing education and support of the patients with T1DM will improve all round care. The development of new drugs and technologies are welcomed but the demonstration of sustained benefit in this challenging group of patients should be clear before their introduction into clinical practice. In the meantime we strive to improve the outcomes of our patients with the most effective treatment and management available. Perhaps, a further review of this cohort in five years time may yield improved results.

M. Wallymhamed, S. Dawes, G. Clarke, S. Saunders, N. Younis and I.A. Macfarlane

10.1 Introduction

Approximately 3% of the United Kingdom population have diabetes mellitus and the prevalence is increasing\textsuperscript{256-258}. Poor diabetes control is related to vascular complications\textsuperscript{259, 260} and patients are admitted to hospital twice as often and stay twice as long as those without diabetes\textsuperscript{261}. Previous surveys indicate that 6–16% of hospital beds are occupied by a person with diabetes and management is often suboptimal\textsuperscript{213, 261-266}. People with diabetes account for around 5% of total NHS resources and 9% of hospital costs\textsuperscript{262}. In 1991 an audit, on a single day, of our hospital revealed that 7.0% of in-patients had diabetes and management was considered inappropriate in 20\%\textsuperscript{213}. Subsequently an in-patient diabetes liaison nurse was appointed and we repeated this audit in 2003 to assess current problems.
10.2 Methods

The study was conducted in a large urban hospital in spring 2003. The hospital departments were unchanged from 1991, serving a population of approximately 400 000 people (surgical, medical, gynaecology, obstetrics and psychiatry specialities). Some departments (Neurosciences, Head and Neck surgery) are regional (Greater Merseyside and North Wales). On one weekday, case records of all patients occupying inpatient beds were reviewed by a consultant diabetologist or specialist registrar and a diabetes specialist nurse. Patients with established diabetes and those newly diagnosed on this current hospital admission were identified. Patients with a raised blood glucose (> 11 mmol/l) this admission, but no previous diagnosis of diabetes were identified. Type 1 or Type 2 diabetes was diagnosed on clinical grounds. Diabetes details and treatments, primary reason for admission, speciality bed occupied and referrals to the hospital diabetes team (nursing or medical) were recorded. Appropriateness of diabetes care was agreed by the whole audit team and recorded, this was the same method used in the original 1991 audit. After 3 months discharge letters (computerised data), of patients with a definite diagnosis of diabetes (previously and newly diagnosed this admission), were reviewed. The admission outcomes, length of hospital stay and if diabetes was mentioned on the discharge summary were recorded.
10.3 Results

On the day, 1191 hospital beds were available for occupancy. Thirty-five were empty and 27 hospital case-notes were absent (e.g. patients in X-ray), leaving 1129 notes for audit. One hundred and twenty-six (11.1%) had a definite diagnosis of diabetes (97%, 122pts Type 2, 3%, 4pts Type 1). Sixty-two per cent were in medical wards, 24% surgical wards, 114 previously diagnosed and 12 newly diagnosed this admission (Table 1). Another 13 patients had a raised random blood glucose (> 11 mmol/l) indicating possible diabetes. The primary reason for admission was diabetes related in 16/126 (12.6%) (8 hyperglycaemia, 1 ketoacidosis, 3 hypoglycaemia, 3 foot ulcers, 1 cellulitis). Other admissions included 16 with macrovascular disease (e.g. myocardial infarction, heart failure, cerebrovascular accident, peripheral vascular disease). The admissions detailed above as ketoacidosis (1pt) and hypoglycaemia (3pt) occurred in those 4 patients with type 1 diabetes. Clearly the bulk of hospital in-patient work in this daily snapshot consisted of patients with type 2 diabetes. The problems of metabolic decompensation in type 1 diabetes are however highlighted by these admissions.

10.3.1 Diabetes management and referrals to the diabetes team

Six patients had been admitted that morning. Of the other 120 patients with definite diabetes, 33 (27.5%) had been referred to the diabetes team this admission (19 to specialist nurses, 4 to medical staff, 10 to both). Management was considered appropriate in 85 (71%), 32 of whom had previously been referred to the diabetes team. Management was considered inappropriate in 35 (29%) and only one of these had been referred. Inappropriate management included: patients with organ failure receiving metformin; high blood sugars with no treatment review or referral to the
team; omission of diabetes medication; inappropriate IV insulin regimens or blood glucose monitoring. In 62 (52%) patients no record of diabetic complications had been made and glycosylated haemoglobin (Hba1c) had been measured in only 29 (24%) patients.

The inappropriate use of intravenous insulin, either in dose or need of such treatment had been identified in another audit conducted around the same time. This audit had particular relevance to patients with type 1 diabetes who were admitted with DKA. It confirmed inadequate documentation, administration and monitoring of IV insulin and its subsequent effect on patients admitted with DKA. It led to the implementation of a DKA protocol within the hospital trust.

10.3.2 Diabetes screening and follow up of raised random blood glucose

Of 1129 records, 191 (17%) had no blood glucose measurement during this admission. Thirteen patients had raised random blood glucose (> 11 mmol/l) without a previous diagnosis of diabetes but this was written in the notes of only 3. The audit team advised repeat measurements and 9 patients subsequently had normal blood glucose levels. Blood glucose remained raised in one patient who subsequently died of a stroke. The other 3 patients did not have repeat measurements. Seven of the 13 patients, including these 3, died in hospital.

10.3.3 Three month follow-up

Ninety eight of the 126 patients with diabetes had been discharged, 12 died in hospital, 3 had transferred to another hospital and 7 remained in hospital. The 12 deaths included: malignancy [6], heart failure [4], myocardial infarction [1], and stroke [1]. Information on the outcome of 6 patients was not found. Discharge
summaries to Primary Care had been completed in only 90/119 (75%) and diabetes was not mentioned at all in 47% of these.

Of the 4 patients with type 1 diabetes, all were discharged home without further consequence. Clinic follow up had been arranged in these cases.

10.3.4 Length of hospital stay
Median hospital stay for the 113 patients with diabetes with data available was 19 days (range 1–300+). Median length of stay for patients who had been referred to the diabetes team was 18 days. During the month of the audit day, the mean length of stay for all hospital patients (with and without diabetes) was 10 days.

10.3.5 Comparison with previous audit (1991)
Between 1991 and 2003, the number of beds available decreased by 25%, particularly in medicine for the elderly, and bed occupancy increased from 83% to 97%. The prevalence of diabetes increased from 7% to 11.1% ($P < 0.01$, Chi-Square) and more had been referred to the diabetes team, 26% v 10% ($P < 0.01$). Diabetes management was considered inappropriate in 29%, more than in 1991 (20%). Median length of stay for patients with diabetes had decreased slightly, 22 days to 19 days (Table 10.1).
**Table 10.1** Comparison of the findings of the 1991 and 2003 audits of hospital in-patients with diabetes

<table>
<thead>
<tr>
<th></th>
<th>1991 (no. beds = 1596)</th>
<th>2003 (no. beds = 1191)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td><strong>Type 2</strong></td>
<td><strong>Type 1</strong></td>
</tr>
<tr>
<td><strong>(n = 5)</strong></td>
<td><strong>(n = 88)</strong></td>
<td><strong>(n = 4)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (26–66)</td>
<td>4 (34–94)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>3 : 2</td>
<td>47 : 41</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>10 (0–44)</td>
<td>7 (0.2–23)</td>
</tr>
<tr>
<td><strong>Diabetes treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet alone</td>
<td></td>
<td>35 (28%)</td>
</tr>
<tr>
<td>OHA’s</td>
<td></td>
<td>66 (52%)</td>
</tr>
<tr>
<td>Insulin only</td>
<td></td>
<td>19 (15%)</td>
</tr>
<tr>
<td>Insulin/OHA’s</td>
<td></td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Overall prevalence of diabetes in hospital (%)</td>
<td>7.0%</td>
<td>11.1%*</td>
</tr>
<tr>
<td>Patients who had been referred to diabetes team (%)</td>
<td>10%</td>
<td>27.5%*</td>
</tr>
<tr>
<td>Management considered inappropriate (%)</td>
<td>20%</td>
<td>29%</td>
</tr>
<tr>
<td>Length of stay (days) (including 16 deaths in 1991, 12 deaths in 2003)</td>
<td>22 (2–300+)</td>
<td>19 (1–300+)</td>
</tr>
</tbody>
</table>

OHA’s, oral hypoglycaemic agents. Results expressed as median (range) or (percentage). *1991 survey v 2003 survey: \( P < 0.01 \) (\( \chi^2 \)).
10.4 Discussion

The audits (1991 and 2003) were on a single day and therefore are subject to random bias such as the severity of illness. Predictably the prevalence of in-patient diabetes has increased (7% to 11.1%, 97% Type 2) most being admitted for reasons other than diabetes. For patients with T1DM the prevalence and reasons for admission remained similar during the interval period of audit. As a whole this group of patients contributes little to the burden of inpatient diabetes care. However it is important, that since these admissions usually reflect metabolic decompensation, that the management is timely and correct.

More patients are now referred to the diabetes team for management advice, mostly to the in-patient diabetes liaison nurse, not present in 1991. However most are still not referred, including newly diagnosed patients and those admitted with diabetes related complications. This is despite a widely distributed written policy for referral. Diabetes management was considered inappropriate in 29% of patients, only 1 of whom had been referred to the diabetes team. Early referral of many of these patients to a specialist nurse may influence quality of care and length of stay\textsuperscript{218, 219} and clinic defaulters can be educated and screened for complications. We do of course recognise the risk of de-skilling the general nurse in using a specialist nurse, and it therefore important to maintain diabetes education for non-specialist staff. The recently introduced ‘Think Glucose’\textsuperscript{267} guidance aims to provide support in this area amongst many of its aims, and it draws much of its information from ‘Focus On: Inpatient care for people with diabetes’\textsuperscript{268}. The UK National Service Framework for Diabetes: Standards Document\textsuperscript{130} and Diabetes UK\textsuperscript{269} stress the important role of a multidisciplinary diabetes team in the care of in-patients. However for every person with diabetes to be reviewed at least once during each admission to this hospital, more specialist nurse time would be required. Currently we are developing
a new system of individual ward-based diabetes link nurses, who receive some specialist training in diabetes. This will help ensure that the in-patient diabetes guidelines are implemented and filter referrals to the specialist service.

Various other deficiencies were revealed by this audit. HbA1c, which is helpful in deciding changes to treatment, had been measured in only 24% of patients with diabetes. There was also a failure to perform screening for diabetes with blood glucose measurements in 17% of all in-patients. Discharge summaries to Primary Care had been completed in only 75% of patients and diabetes was not reported in 47%, an omission which can have an adverse effect on care after discharge. Previous studies also found this. Diabetes was recorded in only 3 of the 12 newly diagnosed patients’ summaries. These shortfalls are due to several factors. Compared to 12 years ago there are fewer hospital beds, increasing numbers of acute admissions, higher bed occupancy and pressure to rapidly discharge patients. In addition the reduction in junior doctors hours of work in the UK leads to lack of continuity of care and extra pressure on senior nursing and medical staff. There is a clear need for constantly educating and reminding junior doctors about the referral criteria, the in-patient guidelines and accurate discharge summary documentation. However guidelines alone will have only a small impact on the quality of care for in-patients without readily available, experienced medical and nursing staff in diabetes care.
11. Intravenous drug abuse and Type 1 diabetes: financial and healthcare implications

S.A. Saunders, J. Democratis, J. Martin and I.A. Macfarlane

11.1 Introduction

Type 1 diabetes (DM) has an incidence of approximately 16 per 100 000 people in the UK. It predominately presents in younger age groups and consequently results in a lifetime of insulin replacement and disease management. Good diabetes control decreases the risk of developing microvascular disease.¹ Crucial in achieving good control is a motivated patient and regular input from a specialist diabetic team.

Intravenous drug abuse (IVDA) can markedly disrupt a normal lifestyle and a healthy regular diet. If type 1 diabetes is also present, a major disruption to the regular routine of insulin injections and food intake often occurs. In recent years we have been aware of frequent hospital admissions by patients with type 1 diabetes who were also intravenous drug abusers (IVDA-DM). We therefore studied the healthcare problems and the financial costs of these hospital admissions in a group of patients admitted over a six-year period.
11.2 Methods

The hospital admission and discharge coding system, which allows cross-referencing of disease codes (ICD-10), was used to identify people with type 1 diabetes and a history of intravenous drug abuse that had been admitted to a large University Teaching Hospital over a six-year period, January 1997 to December 2002. The coding system was also used to identify admissions of IVDA patients due to misuse of opiates or psychoactive drugs. The diabetic patients usually failed to attend diabetes outpatient services and were often impossible to follow up after hospital discharge. Each of the IVDA-DM study group was then matched with two controls (DM) with no history of IV drug abuse that were selected from a register of patients with type 1 diabetes attending the hospital diabetes outpatient clinic, of the same sex, diabetes-duration and age; the matching was blinded to any further information such as HbA1c or hospital attendances. Both these groups were then compared to patients with a history of IVDA alone, for comparison of hospital admissions. For each patient (IVDA-DM) and control (DM) the following data was obtained from every available recorded measurement; HbA1c, creatinine, cholesterol, urine albumin (albustix), blood pressure, insulin dose, weight and body mass index. Mean values for each of these variables for the six-year period were then calculated. Also recorded at their last attendance or inpatient stay were details of micro or macrovascular disease: retinopathy and laser treatment, renal impairment, ischaemic heart disease, myocardial infarction, transient ischaemic attacks, cerebrovascular accident, peripheral vascular disease and other major illnesses. Finally, in December 2002, case notes were reviewed to record the number of deaths.

The total number of inpatient admissions during the six-years of the study (critical care facilities or general medical/surgical ward) was also calculated and from this the financial cost to the Hospital Trust of these admissions was estimated. These
figures were discussed with and kindly reviewed by the finance directorate of this hospital trust to ensure accuracy. Attendance at the outpatient diabetes clinic was also noted. Data was obtained by review of hospital notes and the biochemistry laboratory data system. Local ethics committee approval was granted for this study.
11.3 Statistical Analyses

Individual six-year means and then six-year mean values for the groups were calculated. For normally distributed variables, mean and standard deviation are quoted. For non-normally distributed variables; median and inter-quartile ranges are quoted. Parametric data were compared with unpaired t-tests and non-parametric data using the Mann-Whitney U test and for multiple group analysis the Kruskal-Wallis method for no-parametric data was used; two-sided p-values are quoted for these. Significance was accepted at p values of <0.05. Analysis performed on StatsDirect version 2.2.8 © StatsDirect Ltd.
11.4 Results

Nine patients were identified who had both Type 1 diabetes and a history of IVDA and were compared to eighteen matched controls. The demographic data from the two groups is shown. (Table 11.1) These were in turn compared to 200 IVDA control patients (the total number of patients identified by the coding system between 1997 and 2002) who were unmatched to the other groups. The IVDA-DM group contained one patient who died in the year 2000 and therefore did not have a data set for the full six years.

The six-year data (table 11.1) show large and significant differences between the three groups in inpatient days per year, in both acute medical beds (IVDA-DM 30.4±29.2 days vs IVDA controls 4.9±5.19 vs DM controls 1.1±1.7; p<0.0001) and critical care facilities (IVDA-DM 1.1±1.6 days vs IVDA controls 0.09±1.2 vs DM controls 0; p=0.014). No significant differences between the two groups could be detected in HbA1c, serum creatinine, cholesterol, diastolic blood pressure, and insulin dose per kilogram in 1997 or 2002.

The 9 IVDA-DM patients spent a collective 1513 days in hospital (including critical care facilities) over a six-year period, which approximates to 168 days/patient over six years. In comparison, the IVDA control group of 200 patients spent a total of 5844 days in hospital in six years, approximating to 29 days per patient over 6 years (including critical care admissions). The DM control group spent a total of 109 days in hospital, none of these in critical care facilities, approximating to 6 days per patient over the 6-year study period. The commonest cause for admission in the IVDA-DM group was diabetic ketoacidosis, the rate being 25-fold higher than in the DM controls (Table 11.2). Other common problems were in 6 patients who had, often prolonged, admissions related to the injection of drugs into their groins (major deep vein thrombosis or groin abscesses). Three groin abscesses required formal
incision and drainage, with one patient subsequently dying as a result of septic complications in 2002. The majority (>90%) of admissions for the IVDA controls were due to thrombo-embolic disease (DVT/PE), abscess treatment or localised infections e.g. Cellulitis.

By final case note review in December 2002, 5 of the 9 IVDA group had died. Three deaths occurred out of hospital whilst the remaining two occurred during inpatient stays, one during an admission for diabetic ketoacidosis, one the result of septic complications of a groin abscess. In one of the out of hospital deaths, a patient was found dead at home after recent release from prison, dying as a result of a possible drugs overdose or not taking insulin. Information on the two remaining deaths was not available.

The attendance rate at diabetes outpatient appointments was very poor in the IVDA-DM group and the reasons included; some of these patients already being inpatients, being in prison (at least 3 of this group had spent significant time in prison during the study period), or having no fixed abode. Seven of the 9 IVDA-DM group were receiving opiate (methadone) replacement treatment (mean dose 55 millilitres (1mg/1ml) in 2002) compared to none of the control group. Interestingly the control group, who did not abuse intravenous drugs, admitted the use of cannabis (2 controls) and cocaine use (in one). A significant proportion of the IVDA group were also receiving methadone treatment (mean dose unavailable).

The IVDA-DM group usually defaulted from clinic follow-up, but their inpatient records had more documented retinopathy than the control group and attended for laser treatment less frequently (Table 11.3). They also had more macroalbuminuria and painful neuropathic symptoms. No IVDA-DM patient had documented cardiovascular disease.

Using figures from the financial year 2000-2001, mean daily bed costs for both acute hospital beds and critical care beds can be estimated. There was a huge difference
in the cost of these admissions between the two groups. Estimated mean hospital inpatient admission costs, per patient per year, were IVDA-DM £6769 vs IVDA controls £1100 vs DM controls £213, (table 11.4.) Estimated total admission costs over the six-year study period were: £365 519 IVDA-DM vs £1 320 534 IVDA controls vs £22 999 DM controls. These figures do not take into account any investigation or treatment costs during the patients’ admissions.
11.5 Discussion

This study shows that a small group of type 1 diabetic patients can make huge demands on hospital healthcare services, by repeated admissions with serious medical and diabetic problems associated with IV drug abuse and omission of insulin. Frequent hospital admissions have previously been highlighted in the non-diabetic IVDA population\textsuperscript{270,271} and are again well demonstrated here. The majority of the admissions reported here were due to problems of diabetes control, mainly diabetic ketoacidosis (DKA) as opposed to the problems associated with drug use alone. Hospital surveys of DKA indicate a mortality rate of between 2-5\%\textsuperscript{272,273} and there was one death in this study group during such an admission. Predictably there was also an increased rate of admission for problems that were related to intravenous drug abuse\textsuperscript{274,275}, such as deep vein thrombosis and groin or limb injection site abscesses. One third of the IVDA-DM group underwent incision and drainage or formal debridement of groin/limb abscesses whilst inpatients. One of these patients had an admission lasting 126 days as a result of an abscess, which eventually contributed to that patient’s death. Similar problems were also seen in the IVDA control group who had numerous admissions like this. The average cost of these admissions per patient per year was more than 37 fold higher than the DM control group and 6 fold higher than IVDA controls. These patients also occupied valuable operating-theatre and radiology department time. This increases the overall cost of these admissions; something that our figures do not show. The audit also showed that the IVDA-DM group often failed to attend the diabetic outpatient service after hospital discharge. It is estimated that between 4 and 18\% of diabetic patients fail to attend their regular follow-up appointments\textsuperscript{161,163}, but the IVDA-DM group failed to attend the majority of their diabetes clinic appointments. Many appointments were missed because the patient was unable to be contacted,
probably because they had no fixed abode. A number of the IVDA-DM patients spent long periods of time in prison during the study period, also a problem with the IVDA controls, which also made them unavailable for clinic attendance\textsuperscript{276, 277}. Several also had admissions to other hospitals in the region.

The IVDA-DM group had a higher prevalence of microvascular complications than the DM control group. This occurred in spite of overall similar glycaemic control (HbA1c). Possible explanations for this include the high rate of smoking in the IVDA-DM group (100% vs 38%), which is known to accelerate the development of microvascular complications\textsuperscript{278}. Also the IVDA-DM group also weighed significantly less than the DM control group. No data on this was available for the IVDA controls. This is probably the result of inadequate nutrition and the under-use or missed insulin injections and no doubt the main reason for the high rate of admissions due to DKA. Many of these patients admitted openly omitting insulin for several days, either because they had forgotten or because they had been unable to collect a prescription. The high mortality rate after 6 years in the IVDA group (5/9) compared to no deaths in the controls is perhaps predictable. These patients intravenously inject potentially lethal doses of opiate drugs and also omit insulin, risking fatal DKA.

The current literature contains little on the problems associated with drug abuse in type 1 diabetes\textsuperscript{279} and no study on the problems associated with the intravenous drug use. Also the rate of substance misuse in the general population is not clear, as it tends to be non-declared. Attempts have been made to quantify the degree of substance misuse in hospital admissions\textsuperscript{280}, overall drug misuse occurring in around 5%, with intravenous drug abuse occurring in just over 1% of admissions. Previous estimates have been made of the prevalence of intravenous drug abuse in Liverpool\textsuperscript{281} and a rate of 16.9 per 1000 in the 15-29 year old age group is quoted. The nine IVDA patients reported represent 9.5 % of the 15-29 year old type 1 patients (n= 94) attending this hospital’s diabetes clinic.
It is likely that other urban areas with similar sized hospitals would have a similar population of IVDA diabetics with repeated admissions. We accept however, there may be a small population of similar patients who do not suffer frequent admissions as a result of problems related to either IVDA or diabetes, but since this area has not been studied previously, it would be impossible to say one way or another. We therefore feel that this data is of importance in helping to define the size of the problem. On extrapolating our figures it is possible that 10 chronic IVDA type 1 diabetics may occur in a population of 400,000. This may mean 1250 chronic IVDA type 1 diabetic patients could exist nationally. The cost to the NHS of managing these patients may be in the order of £9 million per year.

Is it possible to improve the situation and reduce the mortality? The frequency and length of admissions are a major problem and reducing these would allow valuable resources to be spent elsewhere and more hospital beds made available for other patients. To prevent DKA directly supervised insulin therapy may help, much like observed administration of methadone at pharmacies or drug addiction clinics. However, this would require dedicated hostel accommodation with trained staff in diabetes management. Most of our IVDA-DM group had no fixed abode and a hostel could provide a short-term housing bridge and also allow specialist nurse and medical input into diabetes management and drug rehabilitation.

The incidence of type 1 diabetes is increasing, and intravenous drug abuse continues unabated. It is therefore likely intravenous drug-abusing type 1 diabetics will continue to provide increasing major social, financial and medical challenges.
<table>
<thead>
<tr>
<th>Table 11.1.</th>
<th>Biochemical and physical variables of control and study groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Mean value for data 1997-2002</strong>*</td>
<td>IVDA-DM</td>
</tr>
<tr>
<td>Number of patients</td>
<td>9 (2 female)</td>
</tr>
<tr>
<td>Age in Dec 2002 (years)</td>
<td>33.3 ± 3.16</td>
</tr>
<tr>
<td>Duration of Diabetes in Dec 2002 (years)</td>
<td>13.7 ± 4.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>10.2 (IQR 1.96)</td>
</tr>
<tr>
<td>Serum Creatinine (µmol/l)</td>
<td>93.0 ± 15.3</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>118.2 ± 12.9</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>73.5 ± 11.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.2 ± 12.0</td>
</tr>
<tr>
<td>Inpatient days/ yr/ patient (Over 6 yrs)</td>
<td>30.4 ± 20.23*,**</td>
</tr>
<tr>
<td>Inpatient days in ITU/HDU/yr (Over 6 years)</td>
<td>1.1 ± 1.6*,**</td>
</tr>
<tr>
<td>Methadone (1mg/ml) dose (mls) N=7</td>
<td>46.3 ± 21.2</td>
</tr>
<tr>
<td>Admitted smoking habit (% of patients)</td>
<td>100</td>
</tr>
<tr>
<td>Outpatient attendance / yr (over 6 yrs)</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>Insulin dose u/kg 1997</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Insulin dose u/kg 2002</td>
<td>1.0 ± 0.2</td>
</tr>
</tbody>
</table>

**KEY:** Data quoted as mean (standard deviation), or median (inter-quartile range): IQR - Inter-quartile range, ND - Not determined, NS - Not significant, KW - Kruskal-Wallis analysis for non-parametric data. MW – Mann-Whitney analysis for non-parametric data. P values significant at <0.05

All recorded data for the study period for each patient was calculated as a mean value, a mean value for each variable was then calculated to gain the group mean value.

* Group significantly different from DM control, ** Group significantly different from IVDA control
Table 11.2  Total separate hospital admissions for diabetes related and non-diabetes problems over 6-year period 1997-2002 in University Hospital Aintree.

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>Hyperglycaemia</th>
<th>Hypoglycaemia</th>
<th>Other Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=18)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td><strong>IVDA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=200)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>638</td>
</tr>
<tr>
<td><strong>IVDA-DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=9)</td>
<td>53</td>
<td>18</td>
<td>2</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 11.3  Microvascular and macrovascular complications, where these details had been recorded in clinical notes

<table>
<thead>
<tr>
<th></th>
<th>Ophthalmology</th>
<th>Renal</th>
<th>Neurological</th>
<th>CVS Events</th>
<th>Mortality (By Dec 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retinopathy</td>
<td>Laser</td>
<td>Persistent Macrolbuminuria</td>
<td>Painful neuropathy</td>
<td>MI/TIA/CVA</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=18)</td>
<td>33.3 %</td>
<td>22 %</td>
<td>16.6 %</td>
<td>33.3 %</td>
<td>5.5 %</td>
</tr>
<tr>
<td><strong>IVDA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=200)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.05%</td>
</tr>
<tr>
<td><strong>IVDA-DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=9)</td>
<td>44 %</td>
<td>11 %</td>
<td>33 %</td>
<td>44.4 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

**Key:** Retinopathy = any retinopathy not having had laser treatment, Macrolbuminuria as >300mg/day respectively, Neuropathy defined as painful neuropathy requiring drug treatment.
Table 11.4  Admissions and costs of admission of control and study groups.

<table>
<thead>
<tr>
<th></th>
<th>Total no. of admission days</th>
<th>No. Days admission to Critical Care</th>
<th>Total cost of Ward Bed £</th>
<th>Total cost of Critical Care Bed £</th>
<th>Total overall cost £</th>
<th>Cost per patient per year £</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Controls (n=18)</strong></td>
<td>109</td>
<td>0</td>
<td>22 999</td>
<td>0</td>
<td>22 999</td>
<td>213</td>
</tr>
<tr>
<td><strong>IVDA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Controls (n=200)</strong></td>
<td>5844</td>
<td>110</td>
<td>1 209 874</td>
<td>110 660</td>
<td>1 320 534</td>
<td>1100</td>
</tr>
<tr>
<td><strong>IVDA-DM (n=9)</strong></td>
<td>1513</td>
<td>46</td>
<td>319 243</td>
<td>46 276</td>
<td>365 519</td>
<td>6769</td>
</tr>
</tbody>
</table>

**Key:** Costs of ward bed is calculated on an average day bed rate financial year 2000-2001 (£211), Critical Care (ITU/HDU) beds calculated on daily bed rate (£1006) for same financial year.
12. Discussion and Further studies
The studies in this thesis demonstrate that the management of patients with T1DM is a complex medical issue. This is a lifelong disease dependent on constant medication use to maintain health. Maintaining health is the minimum goal for diabetes care, as optimally, care should provide the patients with a complication-free life comparable to that of people without diabetes.

There are of course many barriers to achieving this and such barriers are not simple to address. They are wide-ranging and some, as discussed in the literature, are not within the realm of outpatient medical care; falling more within the remit of political, economic and social areas. Since, however, the opportunity to deliver optimum medical care exists within the outpatient setting, then diabetes care teams should strive to engage and involve the patients, provide support and education where needed and offer the most suitable treatments available to maximise health and lower the risk of future complications. The real world delivery of such ideals remains a challenge.

Whilst outpatient care characterises most of the management issues of patients with T1DM a significant number require inpatient care, particularly for acute metabolic disturbances. Also as outcomes improve, diseases of older age emerge. Clearly, ensuring optimal glycaemic control, timely intervention and treatment of complications and facilitated discharge is a service best performed by specialists with an interest in diabetes. The provision of such services within an acute setting, that attain standards of management and the education of non-specialist teams, requires continuation and expansion to achieve the ideals of optimum care.

Regarding the future; the evidence for managing glycaemic and cardiovascular risk has accumulated. The implementation of such measures is becoming increasingly more important. The social context of medical care and the knowledge,
understanding and engagement of the patient become significant in determining how effective such treatments can be.

It is critical to direct further studies into how treatment can be delivered effectively in the real world to patients with diabetes. Developments in forms of medication and their delivery, as well as methods of engaging with patients in the clinic setting should be assessed and audited to see if improvements can be made. Auditing current practice is fundamental to good clinical governance and to delivering optimum care. The goal for future diabetes practice is high quality care delivered with optimum effectiveness.
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14. Publications derived from this thesis

Glycaemic control in a type 1 diabetes clinic for younger adults.

S.A. Saunders, M. Wallymahmed, I.A. Macfarlane.
University Department of Diabetes and Endocrinology, University Hospital Aintree, Liverpool, UK
QJM 2004;97:575-80
Accepted 12th May 2004 © Oxford University Press

Improvements in glycaemic control and cardiovascular risk factors in a cohort of patients with type 1 diabetes over a 5-year period.

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QJM 2009;102:29-34.
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Hospital in-patients with diabetes: Increasing prevalence and management problems

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Intravenous drug abuse and Type 1 diabetes: financial and healthcare implications

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