Use of Insulin in Type II Diabetes Mellitus

Options and Evidence

Master of Science in Pharmaceutical Medicine

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Dissertation Title: Use of Insulin in Type II Diabetes Mellitus: Options and Evidence

Research Objective: To explore which insulin formulations and which regime is the most effective at achieving normoglycaemia in Type II Diabetes Mellitus in patients who are inadequately controlled with maximal oral glucose-lowering therapy?

Background to Research:
The United Kingdom Prospective Diabetes Study (UKPDS) highlighted the progressive nature of type II diabetes, showing that a substantial proportion of patients will eventually go on to require insulin to achieve their glycaemic target. It also helped to establish the benefits of tight glycaemic control in terms of reductions in rates of complications.

In the UK, about 20-25% of type II diabetics are estimated to require insulin within 10 years of diagnosis and it is acknowledged that a greater proportion would probably benefit. In the US, approximately 30-40% of type II diabetics are currently receiving insulin.
In recent years, the number of formulations available for use has increased with the introduction of the rapid acting insulin analogues lispro (Humalog) and aspart (Novorapid), and the first soluble long-acting analogue, glargine (Lantus). Increased choice has increased speculation as to what is the most efficacious regime.

There is currently no consensus as to which formulations or what regime to use. Recent guidance from the National Institute of Clinical Excellence (NICE) asserts “there is no direct evidence to support the use/choice of any one insulin type or regime over another.” There is also uncertainty as to how to most appropriately combine insulin therapy with oral glucose-lowering therapy.

The aim of this research is therefore to ascertain what evidence exists supporting the use of various formulations/regimes, what are the advantages and disadvantages of each preparation, and what is the most appropriate way of combining insulin therapy with oral therapy.

**Methodology**

I shall conduct a literature review looking for randomised controlled trials and meta-analysis of studies exploring the use of insulin in type II diabetes. All formulations, all regimes and all combinations with oral agents shall be included (acknowledging that combining glitazones with insulin is not currently licensed in the UK). I shall use Medline and EMBASE to identify relevant published papers (restricting myself to English language papers). I shall also seek relevant clinical guidelines from professional bodies (such as NICE and the American Diabetes Association) to ascertain their current recommendations and to review literature that they reference.
shall also approach the key pharmaceutical companies in this therapeutic area including Eli Lilly, Aventis and Novo Nordisk in order to attempt to obtain unpublished research in this field.

**Anticipated difficulties**

Given the recent NICE guidance proclaiming no direct evidence to support the use of one insulin type or regime over another, I expect that there will be insufficient available information to enable absolute evidence-based conclusions to be drawn. Furthermore, I expect that the pharmaceutical companies may not be overly forthcoming in providing me with their unpublished studies.

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Thank you to Dr Stephen Thornley for guiding this dissertation to completion and for ensuring my last days in clinical medicine were enjoyable ones. During moments of reflection about the choices I have made, it is having a role model like Stephen that makes the choice to leave medicine a difficult one.

This dissertation has been a much larger undertaking than I ever imagined. And so I finish by acknowledging that.
Overview of Type II Diabetes

Introduction

Type II Diabetes, the most common endocrine disease, is characterised by hyperglycaemia, insulin resistance and relative impairment of insulin secretion. In this Chapter, I shall provide an overview of Type II Diabetes including genetic aspects, pathophysiology, epidemiology and a brief consideration of its morbidity and mortality.

Genetics

There is a strong genetic influence on the development of Type II Diabetes. Among monozygotic twins with one affected twin, the concordance rate is 60-90% (Barnett et al 1981). Klein et al (1996) conducted a population-based study in people with diabetes and found that 39% of patients with older-onset Diabetes had at least one parent with the disease. Bennett (1990) has reported that the lifetime risk for a first-degree relative of a patient with Type II Diabetes is five to ten times higher than that of age and weight matched controls. Further evidence for a strong genetic influence comes from the observation that the prevalence of type II diabetes varies markedly between different ethnic groups living in the same environment (Carter, Pugh, Monterroso 1996).

Various groups have examined more than 250 candidate genes, with interest focused upon genes coding for proteins that might be involved in insulin secretion or action (Kahn 1994). A few cases of Type II Diabetes appear to be associated with mutations in genes coding for insulin, mitochondrial components, the insulin receptor, glucokinase and glycogen synthase – at best these count for only a fraction of cases. It is estimated that mutations in a single gene that result in decreased insulin secretion or action account for less than 5 % of cases of Type II diabetes (Horikawa et al 2000). It is highly likely that most of Type II Diabetes is polygenic and the complex interplay of involved genes currently eludes us.
Pathophysiology

Patients with Type II Diabetes have two physiological defects (Beck-Nielsen, Groop 1994):

i) Abnormal insulin secretion

ii) Insulin resistance in target tissues

Three phases are recognised in the usual clinical sequence. Initially, plasma glucose remains normal despite demonstrable insulin resistance, because insulin levels are elevated. Most authorities believe that insulin resistance is primary and that hyperinsulinaemia occurs as a secondary/compensatory response to the resistance (Foster 1998). In the second phase, insulin resistance worsens so that postprandial hyperglycaemia develops despite elevated insulin concentrations. In the third phase, declining insulin secretion causes fasting hyperglycaemia and overt diabetes.

The relative importance of impaired insulin secretion versus insulin resistance has been examined fairly extensively, but remains somewhat unclear. Weyer et al (1999) demonstrated a decline in insulin-stimulated glucose disposal occurring concomitantly with a decline in the acute insulin secretory response in Pima Indians who went on to develop diabetes. Chen et al (1995) found that impaired insulin secretion preceded insulin resistance in a group of non-diabetic Japanese-American men who went on to develop diabetes. It is possible that insulin resistance becomes more severe with increasing age and weight, thereby unmasking a concurrent defect in insulin secretion in susceptible subjects to cause impaired glucose tolerance and eventually overt hyperglycaemia.

The decline in insulin hypersecretion seen in the third phase may reflect an underlying genetic defect or simply reflect metabolic toxicity in the beta cell. Hyperglycaemia itself may contribute to further progression by a toxic effect on beta cells, possibly by decreasing insulin gene expression (Moran et al. 1997).
Most patients with Type II diabetes are obese, and obesity per se causes insulin resistance. The prevalence of diabetes rises markedly with increasing degrees of obesity (see figure 1). However, nonobese relatives of persons with Type II Diabetes may have hyperinsulinaemia and insulin resistance suggesting that obesity is not the sole cause.

**Fig 1 – Increasing body weight increases risk of diabetes**
Rates of impaired glucose tolerance and diagnosed and undiagnosed type 2 diabetes in the United States adult population according to increase in percent desirable weight from age 25 years to age at maximum adult weight (about 50 years). Data from Harris M., Diabetes Care 1989;12:464
The importance of the combination of genetic and environmental factors in causation of Type II Diabetes is well established. Kahn (1994) studied non-diabetic offspring of two parents with Type II Diabetes and found that their insulin sensitivity was similar to that of normal subjects with no family history of diabetes at near ideal body weight. With increasing degrees of obesity, however, the progressive decrease in insulin sensitivity was much more pronounced in those with the family history of Type II Diabetes (See figure 2)

![Figure 2 - Obesity decreases insulin sensitivity in susceptible subjects](image)

**Fig 2** - Obesity decreases insulin sensitivity in susceptible subjects

Responsiveness to insulin (as assessed from the intravenous glucose tolerance test) according to weight in nondiabetic subjects with no family history of type 2 diabetes mellitus in first-degree relatives and in those with two parents with type 2 diabetes. Data from Kahn C. Diabetes 1994; 43:1066

In association with risk conferred by obesity, lack of physical activity has also been shown to increase the risk of developing Type II Diabetes (see figure 3).
Fig 3 – Importance of body weight and exercise on development of type 2 diabetes.

Adjusted incidence of type 2 diabetes in 5990 men in relation to body mass index and the level of physical activity. Risk of type 2 diabetes was directly related to BMI, while exercised was protective except for men with a BMI below 24 (i.e. healthy weight range) Data from Helmrich S., Ragland D., Leung R., Paffenbarger R. N Engl J Med 1991; 325:147

The presence of insulin resistance in obesity and Type II Diabetes led to a theory of the “thrifty” genotype, in which insulin resistance may improve survival during states of calorific deprivation but lead to diabetes in states of excess (or even adequacy). However, other observations have suggested that the ‘thrifty genotype’ may be induced by malnutrition during foetal life. Rich-Edwards et al (1999) demonstrated an inverse relationship between low birth weight and risk of diabetes mellitus in later life. The relative risk of diabetes decreased progressively from 1.8 for a birth weight of <2.3kg to 0.8 for birth weight >4.5kg.

Type II Diabetes is often accompanied by other conditions including hypertension and abnormal lipid profiles, particularly high serum small-dense low-density-lipoprotein
(LDL) levels and low serum high-density-lipoprotein levels. The constellation of these conditions has come to be known as the metabolic syndrome or syndrome X (Reaven 1988 and DeFronzo, Ferrannini 1991). The World Health Organisation (WHO 1999) has subsequently generated a definition of the metabolic syndrome that can be used for individual diagnosis. This syndrome is associated with marked increase in risk of cardiovascular disease and death.

Metabolic syndrome is defined by the World Health Organization as:

<table>
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<th>At least one of:</th>
<th>Plus at least two of:</th>
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<tr>
<td>- Type 2 diabetes</td>
<td>- Hypertension (BP $\geq$ 140/90 mmHg)</td>
</tr>
<tr>
<td>- Impaired glucose tolerance</td>
<td>- Obesity (BMI $\geq$ 30 kg/m$^2$, or waist-</td>
</tr>
<tr>
<td>- Insulin resistance</td>
<td>- hip ratio $&gt; 0.90$ for men, $&gt; 0.85$ for</td>
</tr>
<tr>
<td></td>
<td>- women)</td>
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<td></td>
<td>- Hypertriglyceridaemia</td>
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<tr>
<td></td>
<td>((\geq 1.7 \text{ mmol/L})) or low serum HDL</td>
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<td></td>
<td>level ($&lt; 0.9 \text{ mmol/L}$ for men, $&lt; 1.0 \text{ mmol/L}$ for women)</td>
</tr>
<tr>
<td></td>
<td>- Microalbuminuria (albumin creatinine ratio $&gt; 2.5 \text{ mg/mmol}$ for men, $&gt; 3.5 \text{ mg/mmol}$ for women)</td>
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**Epidemiology**

It is estimated that worldwide there are now 150 million people with diabetes, and that this number will rise to 300 million by 2025 (Zimmet, Alberti, Shaw 2001). In Australia it has been reported that 7.4% of the population aged 25 or over had diabetes (type 2 in 90%), and that about 50% were undiagnosed (Dunstan et al 2002). Prevalence increases with age, so that more than 20% of the population aged over 60 had Type II Diabetes.
Dunstan et al. found that the prevalence of Type II Diabetes had doubled between 1981 and 2000, and that the total number of cases had increased threefold. Precise figures for the prevalence of the metabolic syndrome are not generally available, but, in Australia, the AusDiab study showed a 16% prevalence of impaired glucose metabolism (impaired glucose tolerance or impaired fasting glucose). This data, which is probably representative of most developed countries, suggests that for every person with Type II Diabetes, there is probably at least two more with the metabolic syndrome.

Much is written about the contribution of modern unhealthy diets to the obesity epidemic in developed countries. Prentice and Jebb (1995) however, have suggested that modern inactive lifestyles are at least as important as diet in the aetiology of obesity and possibly represent the dominant factor (see figure 4).

![Figure 4](https://via.placeholder.com/150)

**Fig 4** - Secular trends in diet (left) and activity (right) in relation to obesity in Britain.

Morbidity and Mortality

Diabetes is associated with a number of microvascular and cardiovascular complications that bring with them substantial morbidity and mortality. The causes of complications in Type II Diabetes are not completely elucidated, but over the past few decades a substantial body of evidence has accumulated linking hyperglycaemia with the development of complications. The presence of complications almost triples the cost of managing diabetes (Colagiuri et al. 2002). The major aim of diabetes management is to prevent complications.

Type II Diabetes is often part of the ‘metabolic syndrome’, which is associated with other risk factors from early in the disease process, including abdominal obesity, hypertension, dyslipidaemia, a prothrombotic state and insulin resistance. These factors interplay to place the patient with Type II Diabetes at particularly high risk.

Macrovacular disease is the major cause of morbidity and mortality in Type II Diabetes (Gaede et al. 2003). Longitudinal studies indicate that the risk of atherosclerotic cardiovascular disease is two to four times greater in patients with Type II Diabetes than in nondiabetic individuals (Krentz, Bailey 2001). Females with Type II Diabetes lose the cardiovascular protection normally conferred by their gender (Kannel, McGee 1979).

Microvascular complications also contribute significant morbidity and are often present at the time Type II Diabetes is diagnosed, even in people with no symptoms. Prevalence’s at diagnosis have been reported to be: retinopathy, about 20%; neuropathy, 9%; and overt diabetic nephropathy, up to 10% (Bate, Jerums 2003).

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD), accounting for 40% of new cases in the Western world. Marshall (2003) reports that 20-30% of patients with diabetes have evidence of overt diabetic nephropathy defined as persistent clinically detectable proteinuria in association with hypertension and reduced glomerular filtration rate. The earliest sign of diabetic renal disease is the presence of urinary albumin excretion, termed microalbuminuria (urinary albumin excretion rate, 30-
300 mg/24 h or 20–200 μg/min; or albumin–creatinine ratio > 2.5 mg/mmol in men and > 3.5 mg/mmol in women). Annual screening of people with diabetes for this complication is recommended. Microalbuminuria identifies individuals at high risk of progressing to macroalbuminuria (albumin excretion ≥ 300 mg/24 h, equivalent to total protein excretion ≥ 0.5 g/24 h), and also at risk of developing ESRD over a period of 10–20 years. Microalbuminuria is also an independent risk factor for cardiovascular disease.

Foot ulcers and amputations are a major cause of morbidity in people with diabetes. They result from the presence of peripheral neuropathy, altered biomechanics in the feet and peripheral vascular disease (PVD). Annual screening of diabetic patients for peripheral neuropathy and PVD is warranted to enable early identification and intervention as needed. A podiatrist should assess patients with evidence of disease and all patients should be educated about daily foot care.

Diabetic retinopathy is the leading cause of blindness in the adult population (VanNewkirk et al 2001). Fong et al (2003) report that up to one third of patients with Type II diabetes have retinopathies at diagnosis, increasing to two thirds within twenty years. In the early stages, the characteristic abnormality is increased vascular permeability. Without treatment, microvascular occlusions may occur, leading to retinal ischaemia and, eventually, the growth of new vessels, termed proliferative retinopathy. Macular oedema may occur at any stage as a consequence of increased vascular permeability. Treatment with laser photocoagulation usually prevents further loss, but generally doesn’t restore vision already lost. Therefore, retinal screening is warranted at least once every two years, to enable early identification of treatable disease before vision is lost.

**Prevention of Complications**

The major goal of therapy in Type II Diabetes is the prevention of the complications above. One of the keys to prevention is early identification of those at risk, and a regular screening program (see figure 5) is warranted in all patients with diabetes.
<table>
<thead>
<tr>
<th>Complication</th>
<th>When to start</th>
<th>Frequency</th>
<th>How to screen</th>
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| **Macrovascular disease** |               | Annually        | □ Ask about symptoms (intermittent claudication, angina [may be atypical] and transient ischaemic attack/stroke)  
 □ Examine pedal pulses, auscultate for bruits, and  
 □ Use a low “threshold” for electrocardiography and exercise stress testing |
| **Microvascular disease** |               |                 |                                                                               |
| Retinopathy             |               | Every 1–2 years | □ Dilated fundus ophthalmoscopy (usually by an ophthalmologist or optometrist) or  
 □ Fundal photography                                                   |
| Nephropathy             | Type 2 diabetes: at diagnosis | Annually       | □ Random spot urine sample for albumin–creatinine ratio* or  
 □ Albumin excretion rate in 24 h or timed overnight urine collection†     |
| Peripheral neuropathy   |               | Annually        | □ Assess protective sensation in feet (eg, with Semmes–Weinstein 10 g monofilament)  
 □ Look for evidence of maldistribution of pressure (eg, calluses), and  
 □ Assess vascular supply and skin integrity                             |
| Autonomic neuropathy    |               | Annually        | □ Ask about symptoms (nausea and vomiting, nocturnal diarrhoea, postural hypotension, erectile dysfunction) |

Fig 5 – Screening for complications of diabetes

Explanatory notes to Fig 5

- Reference range for albumin-creatinine ratio, < 2.5 mg/mmol in men, < 3.5 mg/mmol in women.
- † Microalbuminuria should be confirmed with at least 2 specimens, preferably by measurement of albumin excretion rate. False positive results occur with recent exercise, urinary tract infection, fever, marked hypertension, marked hyperglycaemia, congestive cardiac failure and haematuria.

I shall address the evidence supporting the aggressive treatment of hyperglycaemia in the next chapter. Much of the intervention in diabetics is aimed at risk reduction, with therapeutic targets other than glucose control. There is good evidence supporting treatment of hypertension (UKPDS 38 1998, Hanson et al 1998 and HOPE 2000) and dyslipidaemia (4S 1994, Sacks et al 1996, HPS 2002 and Sever et al. 2003). The HOT study (Hanson et al 1998) also provided evidence for the use of low dose aspirin for all people with diabetes and another cardiovascular risk factor, such as dyslipidaemia or hypertension. Lifestyle measures including dietary modification, regular exercise and smoking cessation should also be advocated (Hu et al 2001 and Tuomilehto et al 2001).
REFERENCES


Normoglycaemia as a therapeutic target

Hyperglycaemia and risk of vascular complications
An association between the complications of diabetes and elevated blood glucose was first postulated in the early part of last century. However it has only been in the last few decades that a substantial body of evidence has accumulated directly linking hyperglycaemia with the development of complications (Genuth 1995). Klein et al (1994) noted a direct correlation between the degree of glycaemic control and the incidence and progression of retinopathy in a study of 1516 patients with diabetes (682 patients with diabetes onset <30y.o and 834 patients with onset>30y.o). Gilbert et al (1993) demonstrated a similar relationship between glycaemic control and renal disease in Type II Diabetics. Epidemiological studies suggest that microvascular disease occurs with a fasting blood glucose (FBG) >7.8mmol/L and macrovascular disease occurs when it is >6.1mmol/L (Fuller at al 1980 and Harris 1989). Establishing a relationship between glycaemia and complications does not necessarily mean that improving glycaemic control will improve outcomes. I shall address the evidence confirming that this does occur below.

The Case for Tight Glycaemic Control in Type I Diabetes
The sentinel paper in Type I diabetes was the Diabetes Control and Complications trial (DCCT 1993) which provided convincing evidence of the benefits of tight control. This study involved 1441 patients with Type I Diabetes and randomly assigned them to receive either intensive therapy aimed at achieving near normal glucose levels or conventional therapy. In those without evidence of retinopathy at baseline, intensive therapy reduced the adjusted mean risk for developing retinopathy by 76%. In a secondary prevention cohort (with evidence of retinopathy at baseline), progression of retinopathy was slowed by 54%. The occurrence of microalbuminaemia was reduced by 39%, albuminaemia by 54% and clinical neuropathy by 60% in the intensive therapy group. The major adverse event associated with intensive treatment was a two-to-three fold increase in the occurrence of severe hypoglycaemia. Significantly, there was no discernable glucose threshold, with a continuous reduction in complications as glycaemic
levels approached the normal range. Intensive therapy also reduced cardiovascular events in the DCCT, but the difference was not statistically significant.

**The Case for Tight Glycaemic Control in Type II Diabetes**

Until relatively recently, evidence that tight glycaemic control reduced complications in Type II Diabetes was lacking. Before the United Kingdom Prospective Diabetes Studies (UKPDS 33 and 34 1998), only three randomised controlled trials existed that attempted to assess the benefit of tight glycaemic control on the rate of complications (ADA 2001).

The first RCT (UGDP 1978) failed to show a benefit in new-onset Type II Diabetics. It followed 1000 patients assigned different therapies for about 5.5 years and found no evidence that improved glycaemic control reduced the risk of vascular endpoints. Of note, a major concern that arose from this study was the observation that the sulfonylurea (tolbutamide) and a biguanide (phenformin) used to control glucose were actually associated with increased cardiovascular mortality. This unexpected finding produced new hypotheses as to how some of the glucose lowering drugs may increase cardiovascular risk (Smits, Thien 1995).

The first RCT evidence supporting tight glycaemic control was a small study in 110 Japanese patients (Ohkubo et al. 1995). It compared multiple insulin injections (goal of HbA1c<7.0%) with conventional insulin treatment. Patients were divided into a primary prevention cohort, with no evidence of retinopathy or nephropathy at baseline, and a secondary prevention cohort, with evidence of simple retinopathy and urinary albumin excretion>30mg/day. The intensively treated group achieved improved glycaemic control (HbA1c 7.1% vs 9.4%), which was associated with significant reductions in microvascular complications (retinopathy and nephropathy) similar to that observed in the DCCT. Results in the primary prevention cohort were that after six years, tighter control reduced the rate of development of retinopathy from 32.0% to 7.7 %, and the rate of nephropathy from 28% to 7.7%.
The third RCT (Abraira et al. 1997) randomised 153 men to intensive or conventional therapy. It achieved a 2.07% difference in HbA1c between the two groups but failed to demonstrate a significant difference in cardiovascular events after a follow-up period of 27 months.

**The United Kingdom Prospective Diabetes Study (UKPDS 33 1998)**

The UKPDS (UKPDS 33 and UKPDS 34 1998) provided the evidence that had been lacking in support of tight glycaemic control. It is the largest and longest study that has ever been conducted on Type II Diabetics. Over 4000 patients were recruited in 23 centres around the UK between 1977 and 1991. Patients were followed for an average of ten years to determine:

i) whether intensive therapy to lower blood glucose would result in clinical benefits and

ii) whether the use of various sulfonylurea drugs, metformin or insulin have specific therapeutic advantages or disadvantages over one another.

Patients who were hypertensive were also randomised to either ‘tight’ or ‘less tight’ blood pressure control to ascertain the benefits of blood pressure lowering. I shall not be considering the results of this arm here.

UKPDS 33 randomised 3867 newly diagnosed patients with Type II Diabetes with a median age of 54, who after 3 months diet treatment had a mean of two fasting plasma glucose (FPG) of 6.1-15.0mmol/L. These patients were randomly assigned to intensive treatment with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide) or insulin, or conventional treatment with diet. The target for the intensive treatment arm was a FPG<6.0mmol/L. In the conventional treatment arm, the aim was the best achievable FPG with diet alone, unless the patient had symptoms of hyperglycaemia or a FPG>15.0mmol/L

Over ten years intensive therapy achieved a median HbA1c of 7.0%(6.2-8.2) compared to 7.9% (6.9-8.8) in the conventional therapy group, corresponding to an 11% reduction (see figure 1).
Glycaemic control, estimated from the median HbA1c value, in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study on conventional versus intensive therapy. The circles represent data for all patients while the lines represent data for patients followed for ten years. Data from UKPDS 33 Lancet 1998;352:837

This was associated with a 12% risk reduction (p=0.029) for ‘any diabetes-related endpoint’. Most of this reduction was due to a 25% reduction (p=0.0099) in the overall microvascular complication rate. A 16% reduction in the risk of combined fatal and nonfatal myocardial infarction and sudden death was observed, but this failed to reach statistical significance (p=0.052). There was no difference for any of the three aggregate endpoints (any diabetes-related endpoint, diabetes-related death or all-cause mortality) between each of the intensive treatment groups. A table comparing the two treatment groups’ rates of single and aggregate endpoints is presented below (see figure 2).
Table 1 - Proportion of patients with aggregate and single endpoints by intensive and conventional treatment and relative risks.


Fig 1 – Proportion of patients with aggregate and single endpoints by intensive and conventional treatment and relative risks.
Overall intensive therapy was considered safe and well tolerated. Patients in the intensive group had more hypoglycaemic episodes than those in the conventional group on both types of analysis (both p<0.0001). The rates of major hypoglycaemic episodes per year were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide, and 1.8% with insulin.

Weight gain was significantly higher in the intensive group (mean 2.9 kg) than in the conventional group (p<0.001), and patients assigned insulin had a greater gain in weight (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg).

The concern about increased risk of cardiovascular death with sulfonylureas raised by UGDP (1978) was not substantiated by UKPDS 33 (1998). No difference in the rates of myocardial infarction or diabetes-related death was observed between the groups assigned sulfonylurea or insulin therapies.

Epidemiological analysis of the data showed a continuous relationship between risks of microvascular complications and glycaemia, such that for every percentage point decrease in HbA1c there was a 35% reduction in risk of complications (ADA 2001). It has also demonstrated a continuous association between the risk of cardiovascular complications and glycaemia, with each percentage point fall in HbA1c equating to a 25% reduction in diabetes related deaths, a 7% reduction in all-cause mortality, and an 18% reduction in combined fatal and non-fatal MI.

**UKPDS 34 (1998) – The Use of Metformin**

UKPDS also evaluated the use of Metformin in overweight patients with Type II Diabetes. Of the 4075 patients recruited to UKPDS, 1704 were overweight (>120% ideal body weight). Of these 753 were included in a randomised controlled trial comparing conventional dietary treatment with metformin, aiming for a FPG<6mmol/L. A secondary analysis was also performed comparing the patients allocated metformin (n=342) with the 951 overweight patients allocated to intensive treatment with sulfonylureas or insulin in UKPDS 33. A supplementary RCT was also conducted in 527 patients who had raised
FPG on maximum sulfonylurea therapy. This group were randomised to continuing sulfonylurea therapy alone or addition of metformin in equal numbers.

Median HbA1c was 7.4% for metformin compared with 8.0% for conventional treatment. Treatment with metformin resulted in risk reductions of 32% for any diabetes related endpoint (p=0.002), 42% for diabetes related death (p=0.017), and 36% for all-cause mortality (p=0.01). Metformin also showed a greater effect than all other intensively treated groups for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021 and stroke (p=0.032) (see figure 3).

**Fig 3 – Metformin in overweight patients with Type II Diabetes**
Kaplan-Meier plots of any diabetes-related endpoint in 753 overweight patients with type II diabetes in the UKPDS who were randomly assigned to either metformin or to conventional treatment with diet. Another 951 overweight patients received intensive therapy with a sulfonylurea or insulin. Data from UKPDS 34. Lancet 1998; 352:854
An unexpected finding was that addition of metformin to patients with persistently elevated FPG on sulfonylureas was associated with a 96% increase in diabetes-related death ($p=0.039$) and a 60% increase in all-cause death ($p<0.041$). It is difficult to know how to interpret this finding. The lack of placebo control, the significant cross-over rate (25% of the group randomised to sulfonylurea were given metformin) and the inability to employ masking in this substudy have all raised doubts over the validity of these detrimental findings. Epidemiological analysis conducted by the investigators did not corroborate an association between combined therapy and diabetes-related deaths but confidence intervals were wide.

Another finding of note is that metformin failed to achieve a statistically significant reduction in microvascular complications, though the trend was for a risk reduction of 29% ($p=0.19$).

Metformin would seem to be the first line treatment of choice in obese patients with Type II Diabetes – indeed, it was the only treatment that achieved a significant reduction in cardiovascular outcomes. This may relate to the absence of weight gain with metformin use and/or to some beneficial effect of metformin on the metabolic syndrome. Further study is warranted to explore any possible detrimental effects when metformin is added to therapy with sulfonylureas.

**Macrovascular Disease – an Outstanding Question?**

As detailed above, there is adequate evidence that tight glycaemic control significantly reduces the risk of occurrence and progression of microvascular complications. There are however, conflicting data on the importance of glycaemic control on the development of macrovascular disease in type II Diabetes. A prospective study in Finland, which followed 1069 nondiabetic and 229 subjects with Type II Diabetes for 3.5 years, found that a high HbA1c was a strong predictor of cardiovascular death and of all CHD events, particularly in women (Kuusisto et al. 1994). In contrast, the Patient Outcomes Research Team (Meigs et al 1997) found the prevalence of cardiovascular disease was constant
across increasing quartiles of HbA1c values. Cardiovascular disease was associated with traditional risk factors and with the duration of diabetes.

In UKPDS 34 (1998) Metformin achieved a 39% lower risk (p=0.010) of myocardial infarction than conventional treatment. This compared to a non-significant 16% risk reduction (p=0.052) for patients treated with insulin or sulfonylureas in UKPDS 33 (1998).

The VACSDM study (Abraira et al 1997) of 153 men with Type II Diabetes found a non-significant (p=0.1) increased risk of new cardiovascular events in patients receiving intensive therapy (multiple injections +/- a sulfonylurea) compared to those on a single insulin injection daily. It is worth noting that this was a much smaller trial than UKPDS and that the diabetic patients in the VACSDM were not newly diagnosed and had a higher prevalence of cardiovascular risk factors.

There is evidence that the relationship between blood glucose levels and cardiovascular risk extends into the nondiabetic range (Coutinho et al 1999). Khaw et al (2001) followed a cohort of 4662 men aged between 45 and 79 and found all cause mortality and cardiovascular deaths were significantly higher among those with an HbA1c in the high end of normal compared with those with a HbA1c<5.0% (see figure 4). An increase of 1% in HbA1c was associated with a 28% (P<0.002) increase in risk of death independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking habit.

Further evidence of the detrimental cardiovascular effects of poor glycaemic control is provided in a relatively short-term study by Iribarren et al (2001). They followed almost 50000 predominantly Type II Diabetic patients with no heart failure at baseline for a mean of 2.2 years and found each 1% increase in HbA1c was associated with an 8% increased risk of heart failure. A HbA1c >10% increased the risk of heart failure by 1.6-fold compared with a HbA1c<7%.
Fig 4 – HbAlc as a predictor of mortality


There is a large evidence base demonstrating that hyperglycaemia is a strong predictor of cardiovascular risk. To date randomised controlled trials have failed to convincingly demonstrate that tight glycaemic reduces this risk, but it is worth noting that the largest of them (UKPDS 1998) did show a statistically non-significant trend in the direction of risk reduction. Early concerns about a potential to increased cardiovascular risk with sulfonylureas and insulin therapy have not been substantiated by UKPDS.

Conclusions

Tight glycaemic control in Type II Diabetics is associated with a decreased risk of microvascular complications. Outcomes improve for every 1% drop in HbAlc and there does not seem to be a threshold effect. Benefits in terms of macrovascular complications
are yet to be convincingly established, but concerns about a possible detrimental effect have now been largely allayed.

We now have a greater understanding of the progressive nature of Type II Diabetes and the fact that this necessitates a combination of therapies if glycaemic targets are to be attained. The use of multiple therapies creates cost considerations both for patients and health care systems alike, but the costs of therapy must be offset against the savings obtained through avoidance of complications.

We can feel confident that tight glycaemic control can be attained safely. However, we must be mindful of the observed increased risk of hypoglycaemic events in the more intensively treated patients. Weight gain associated with certain therapies may also have implications for patient acceptability of intensive treatment regimes. Each patient should be encouraged to get their HbA1c as close to normal as is practically possible.

The American Diabetes Association (ADA) currently recommends a target of less than 7.0 percent for most patients, while the American Academy of Clinical Endocrinologists (AACE) and the European Association for the Study of Diabetes (EASD) both recommend a target of HbA1c less than 6.5 percent. Given that the risk of all cause death and cardiovascular death is higher among those with HbA1c between 5.0 to 6.0 percent than it is for people with HbA1c less than 5 percent (Khaw et al 2001), it is likely that recommended targets will continue to fall in the future.

Finally, it would be remiss not to highlight the fact, that glycaemic control is simply one aspect of the management of patients with Type II Diabetes. Vigorous cardiac risk reduction with advice on smoking cessation, appropriate use of aspirin, tight blood pressure control, management of dyslipidaemia, lifestyle modifications including diet and exercise, and use of angiotensin converting enzyme inhibitors when appropriate, should all be considered as part of the management of patients with Type II Diabetes. It is only through a multifaceted approach that we can hope to optimise the care and improve the quality of life of patients with Type II Diabetes.
REFERENCES

8. UKPDS 33 (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with


European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk).


Pharmacologic Treatment of Blood Glucose

Diet, weight reduction and exercise should all be part of the measures used to improve glycaemic control in Type II Diabetes. These measures can be very effective, but compliance is not sustained in most patients (Schneider et al 1992 and Uusitupa et al 1993). As a result, pharmacologic treatment is eventually required in most patients.

There are currently four therapeutic drug options for Type II Diabetes:

1) Increase insulin release with a sulphonylurea or meglitinide
2) Increase insulin responsiveness with a biguanide (metformin) or a thiazolidinedione.
3) Modify intestinal absorption of carbohydrate with an alpha-glucosidase inhibitor, or absorption of fat with a lipase inhibitor.
4) Administer exogenous insulin.

Sulphonylureas

Clinical Use

Sulphonylureas are the most widely used drugs for the treatment of patients with Type II Diabetes (Bressler, Johnson 1997). They may be used as monotherapy, or in combination with other oral hypoglycaemic drugs or insulin. Most patients who are normal weight or only moderately obese are begun on a sulphonylurea. A 20% lowering of blood glucose concentrations should be expected (Groop 1992, Herman et al 1994 and UKPDS 13 1995).

The sulphonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present. Several sulphonylureas are available and their efficacies are felt to be fairly similar. Choice is therefore determined by cost, availability, side effects and duration of action, as well as the patient's age and renal function. Although the manufacturers recommend doses as high as 20-40mg/day for glipizide or glibenclamide, doses above 10mg/day usually have little further effect (Stenman et al 1993).
Pharmacokinetics

Glipizide, glibenclamide and glimepiride are so-called second-generation sulphonylureas. They have structural characteristics that enable them to be given at much lower doses than the first generation drugs.

The long acting sulphonylureas chlorpropamide, glimepiride and glibenclamide can be given once daily. They cause greater suppression of overnight hepatic glucose output, thereby lowering fasting blood glucose more. They are however associated with a greater risk of hypoglycaemia and are best avoided in elderly patients, where short acting alternatives gliclizide or tolbutamide should be used instead (Shorr et al 1996).

Side Effects

Sulphonylureas are usually well tolerated. Hypoglycaemia is the most common side effect and is more common with long-acting sulphonylureas as stated above. Patients should be educated about the symptoms of hypoglycaemia and what steps to take if it occurs.

Other infrequent side effects include nausea, skin reactions and abnormal liver function tests. Chlorpropamide has two unique effects: it can cause an unpleasant flushing reaction after alcohol ingestion by inhibiting acetaldehyde metabolism (Groop et al 1984); and it can cause hyponatraemia (Kadowaki et al 1983). As a result of these occurrences (and the higher risk of hypoglycaemia) chlorpropamide should no longer be recommended.

Meglitinides

The meglitinides, repaglinide and nateglinide, are short acting glucose lowering drugs that may be used as monotherapy or in combination with metformin. They are structurally different from sulphonylureas but act similarly by regulating ATP-dependent potassium channels in pancreatic beta-cells, thereby increasing insulin secretion (Fuhlendorff et al 1998).
The clinical efficacy of repaglinide is similar to that of the sulphonylureas (Wolffenbuttel, Landgraf 1999). It can also be given in combination with metformin (Moses et al 1999). Doses are taken before each meal and should be skipped if a meal is missed (Moses et al 2001 and Schmitz et al 2002).

Repaglinide is considerably more expensive than the sulphonylureas and is yet to demonstrate any therapeutic advantages over them. This has limited its use in clinical practice to date.

The Food and Drug Administration have approved Nateglinide, a new drug in this class, for monotherapy or in combination with metformin. In the UK it is only indicated in combination with metformin. As monotherapy it is less effective than metformin, but combination therapy has been shown to be more effective than either drug alone (Horton et al 2000). In a comparison study with glibenclamide, both drugs produced similar degrees of overall mealtime glucose control; nateglinide had a greater effect on mealtime glucose excursions, while glibenclamide had a greater effect on fasting blood glucose (Hollander et al 2001).

**Biguanides (Metformin)**

*Actions*

Metformin is the only biguanide that is currently available. It is particularly useful in obese patients with Type II Diabetes since it does not increase insulin secretion. It is effective only in the presence of insulin, and its major effect is to increase insulin action (Bailey, Turner 1996). The mechanism by which metformin increases insulin action is not known. Postulated mechanisms include suppression of hepatic glucose output, increased insulin-mediated glucose utilisation in peripheral tissues and an antilipolytic effect that lowers serum free fatty acid concentrations, thereby reducing substrate for gluconeogenesis (Bailey 1992 and Stumvoll et al 1995). Metformin also increase intestinal glucose utilization via nonoxidative metabolism. The lactate produced by this process is largely metabolised in the liver as a substrate for gluconeogenesis, which may protect against hypoglycaemia.
Clinical Use

Metformin is most often used in obese patients, because it promotes modest weight reduction or at least weight stabilisation (see figure 1). In the UKPDS 24 (1998), for example, among obese patients in the primary diet failure group, those allocated to insulin had a greater mean increase in body weight (10.4 kg) than those allocated to a sulfonylurea (3.7 kg) or metformin (no significant change).

![Weight change with drug therapy in Type II Diabetes](image)

Metformin typically lowers blood glucose concentrations by 20%, a response similar to that achieved with a sulphonylurea (Hermann et al 1994). The US Multicentre Metformin Study Group also found that patients not well controlled with glibenclamide alone had a substantial improvement in fasting blood glucose when metformin was added (DeFronzo,
Goodman 1995). The main indication for combination therapy is an inability to achieve glycaemic control with either drug alone, particularly in a patient who does not want to take insulin.

In addition to avoidance of weight gain, metformin has two other advantages over the sulphonylureas. It is less likely to cause hypoglycaemia and it has prominent lipid lowering activity, resulting in a decrease in serum triglyceride and free fatty acid concentrations, a small decrease in LDL-cholesterol and an increase in HDL-cholesterol (Wu et al 1990). These are however offset against two disadvantages: the risk of lactic acidosis and prominent gastrointestinal side effects.

**Pharmacokinetics**

Metformin is absorbed rapidly from the small intestine, with peak plasma concentrations obtained in two hours. It is not bound to plasma proteins, is not metabolised, and is rapidly excreted in the urine with a half-life of 1.5-4.9 hours.

Metformin is available as a 500 and 850mg tablets and should be taken with meals. Starting dose is 500mg daily increased slowly as necessary to a maximum of 2550mg daily (850mg tds). It is important to start low and increase gradually to decrease the likelihood of gastrointestinal complications, which have the potential to impact greatly on patient compliance.

**Side effects**

The most common side effects are gastrointestinal, including a metallic taste in the mouth, anorexia, nausea, abdominal discomfort and diarrhoea. These symptoms are usually mild, transient and reversible after dose reduction or discontinuation.

Metformin also reduces absorption of Vitamin B12 in up to 30%, which may lower serum B12 levels and rarely, lead to megaloblastic anaemia – this can be corrected by oral administration of calcium (Bauman et al 2000).
Lactic Acidosis

Metformin may cause lactic acidosis. Stang et al (1999) reported the incidence of lactic acidosis in patients taking metformin to be 9 per 100 000 person-years. This compares with a rate of 40-64 per 100,000 patient years in patients taking the old biguanide, phenformin. However, in a systematic review of 176 studies including 35619 person-years of metformin therapy, there were no cases of lactic acidosis.

Certain conditions predispose to serious lactic acid accumulation and are therefore relative or absolute contraindications to metformin:

- renal insufficiency
- liver disease or alcohol abuse
- heart failure
- past history of lactic acidosis
- severe infection with decreased tissue perfusion
- hypoxia
- haemodynamic instability
- serious acute illness
- age > 80 years

Metformin should also be stopped 48 hours prior to receiving intravenous iodinated contrast material due to potential nephrotoxicity of iodine. In a review of 110 published cases of metformin associated lactic acidosis, nine occurred in patients with contrast-induced renal failure (Sirtori, Pasik 1994).

Most cases of lactic acidosis associated with metformin have occurred in patients with shock or tissue hypoxia (Lalau et al 1995). However it can occur in patients with normal renal and hepatic function (Pepper, Schwartz 1997).

Thiazolidinediones

There are currently two thiazolidinediones available on the market: rosiglitazone (Avandia) and pioglitazone (Actos). The first drug in this class, troglitazone (Rezulin),
was removed from the market because it caused liver dysfunction and in some cases liver failure.

These drugs increase insulin sensitivity by acting on muscle and liver to increase glucose utilisation and decrease glucose production (Nolan et al 1994 and Iwamoto et al 1996). They also increase insulin secretion in response to glucose, at least in patients with impaired glucose tolerance (Cavaghan et al 1997). This finding suggests that the thiazolidinediones can improve the early beta-cell dysfunction that occurs in patients with impaired glucose tolerance.

Clinical Use-Monotherapy
Most of the available efficacy data is for troglitazone, which is no longer available. It is felt that the efficacy of all three drugs is similar, but no comparative studies have been undertaken (McCulloch 2003).

Aronoff et al (2000) conducted a six-month trial of monotherapy with three dose levels of pioglitazone and found significant reductions in HbA1c (range -1.0 to -1.6% compare with placebo) and fasting blood glucose (-2.2 to -3.6mmol/L compared with placebo). There were also significant decreases in triglycerides, increases in HDL cholesterol, and only small changes in total cholesterol and LDL. The overall adverse event profile of pioglitazone was similar to that of placebo and no evidence of hepatotoxicity was found.

A six-month trial of rosiglitazone demonstrated similar efficacy (Lebovitz et al 2001). Rosiglitazone (2 and 4 mg bd) decreased mean HbA1c relative to placebo by 1.2 and 1.5% respectively, and reduced fasting plasma glucose concentrations relative to placebo by 3.22 and 4.22 mmol/L, respectively.

Rosiglitazone and pioglitazone have similar effects on glycaemic control, but their effects on serum lipids may be slightly different. Khan et al (2002) randomised 127 diabetic patients previously treated with troglitazone to either pioglitazone or rosiglitazone for four months. Glycaemic control and weight gain (2kg) were the same in both groups.
However, serum total and LDL cholesterol decreased with pioglitazone but not with rosiglitazone.

Clinical Use – Combination therapy

Fonseca et al (2000) evaluated the use of rosiglitazone in 348 patients who were inadequately controlled with metformin alone. Patients were randomised to continued metformin alone or metformin in combination with rosiglitazone (4mg/d or 8mg/d). Over six months, the mean levels of HbA1c decreased by 1.0% in the 4 mg/d metformin-rosiglitazone group and by 1.2% in the 8 mg/d metformin-rosiglitazone group and fasting plasma glucose levels by 2.2 mmol/L and 2.9 mmol/L compared with the metformin-placebo group (P< 0.001 for all).

Raskin et al (2001) conducted a similar study evaluating rosiglitazone in combination with insulin. 319 type 2 diabetic patients with mean baseline HbA1c ≥ 7.5% on twice-daily insulin therapy (total daily dose ≥ 30 U) were randomised to 26 weeks of additional treatment with rosiglitazone (4 or 8 mg daily) or placebo. Treatment with rosiglitazone 8mg plus insulin resulted in a mean reduction from baseline in HbA1c of 1.2% (P < 0.0001), despite a 12% mean reduction of insulin dosage. However, post-marketing studies of this combination have reported an increased incidence of heart failure, suggesting that use of this combination therapy be limited (FDA 2002). Indeed, this combination therapy is not a licensed indication in the UK.

Kipnes et al (2001) evaluated the efficacy of combined pioglitazone and sulphonylurea therapy in a study of 560 patients with inadequate glycaemic control on sulphonylurea therapy. The patients who received pioglitazone (15 or 30mg) plus the sulphonylurea had significant decreases in HbA1c (0.9 and 1.3% lower respectively) than those who
received sulphonylurea plus placebo. Pioglitazone was also observed to have favourable impact on serum lipids.

**Weight gain**

All of the thiazolidinediones cause weight gain (see figure 2). It is both dose-dependant and time dependent. The weight gain is caused by both proliferation of new adipocytes and redistribution of fat stores. Fluid retention may also be a contributing factor.

![Graph showing weight gain with thiazolidinediones](image)

**Fig 2 – Weight gain with thiazolidinediones.**


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**Hepatotoxicity**

As mentioned above, troglitazone was removed from the market because of reports of severe hepatocellular injury. Rosiglitazone was not associated with hepatotoxicity in clinical trials involving approximately 5000 patients (Lebovitz, Kreider, Free 2002). There have however been case reports of hepatic toxicity in at least two patients receiving rosiglitazone (Forman, Simmons, Diamond 2000 and Al-Salman et al 2000). Two cases of hepatotoxicity have also been reported with pioglitazone (Maeda 2001 and May et al 2002). Monitoring of liver function is thus recommended every two months during the first year of therapy and periodically thereafter.

**Alpha-Glucosidase Inhibitors (Acarbose)**

Acarbose is the only available alpha-glucosidase inhibitor in the UK. It acts by inhibiting the upper gastrointestinal enzymes (alpha-glucosidases) that convert carbohydrate into monosaccharides in a dose dependent fashion. This effect slows absorption of glucose, which leads to a lower postprandial peak in blood glucose. Meneilly et al (2000) also found that acarbose increased insulin sensitivity in a group of 45 elderly patients with type II Diabetes. It has a small but significant effect in lowering blood glucose and may be used as monotherapy or in combination with metformin or sulphonylureas.

**Efficacy**

Several trials have demonstrated the efficacy of acarbose in patients with Type II Diabetes. Hoffman et al (1994) randomised 96 patients inadequately controlled with diet to receive glibenclamide, acarbose or placebo. Compared with the placebo, both drugs showed the same mean efficacy on fasting blood glucose (-1.4 mmol/L with acarbose, -1.6 mmol/L with glibenclamide), 1hr postprandial blood glucose (-2.2 mmol/L with acarbose, -1.9 mmol/L with glibenclamide), and HbA1c (-1.1% with acarbose, -0.9% with glibenclamide).

Another study by Chiasson et al (1994) recruited 354 patients with non-insulin-dependent diabetes mellitus; 77 were being treated with diet alone, 83 with diet and metformin, 103
with diet and sulfonylurea, and 91 with diet and insulin. Patients in each treatment group were randomly assigned to either acarbose or placebo for 1 year. The addition of acarbose in each of these groups reduced the mean post-prandial blood glucose concentration by 3.5mmol/L. Corresponding decreases in HbA1c levels occurred; these were 0.9% in the diet alone group (P = 0.005), 0.8% in the metformin group (P = 0.011), 0.9% in the sulfonylurea group (P = 0.002), and 0.4% in the insulin group (P = 0.077).

Acarbose may also have beneficial effects on serum lipid concentrations. Hoffman and Spengler (1997) studied a group of 96 patients randomised into 3 groups and treated for 24 weeks with acarbose, 3 x 100 mg/day, or metformin, 2 x 850 mg/day, or placebo. Efficacy was similar between metformin and acarbose; HbA1c was 9.8% with placebo, 8.5% with acarbose, and 8.7% with metformin. The acarbose group had a 27% decrease in the ratio of LDL-cholesterol to HDL-cholesterol, due to both a decrease in LDL (4.1 to 3.2mmol/L) and an increase in HDL (1.4 to 1.6mmol/L). By comparison, the metformin group had no change and the placebo group had a 14% increase in the serum LDL/HDL ratio.

**Side effects**

Gastrointestinal side effects are very common with use of acarbose and have considerably limited its use. The occurrence of flatulence and diarrhoea has been observed to limit patient compliance in clinical trials (Holman, Cull, and Turner 1999). Careful titration of acarbose is needed in order to minimise these adverse effects.

**Lipase Inhibitors (Orlistat)**

Orlistat (Xenical) is a minimally absorbed drug that inhibits pancreatic and gastric lipases, blocking absorption of approximately 30% of ingested fat. Two studies in obese subjects over two years have demonstrated orlistat to achieve significantly more weight loss than placebo (see figure 3) (Sjostrom et al 1998 and Davidson et al 1999).
Fig 3 – Weight loss in obese subjects on orlistat

Mean body weight change during two-years treatment with diet plus orlistat or placebo. The patients initially received a reduced energy diet and, at one year, a maintenance diet. Orlistat therapy was associated with more weight loss and less weight regain. Data from Davidson M., Hauptman J., DiGirolamo M et al. JAMA 1999; 281:235.

In diabetic patients, the weight loss induced by orlistat is associated with improved glycaemic control. Hollander et al (1998) randomised 391 obese subjects with type II diabetes on sulphonylureas to receive either orlistat 120mg tds or placebo. After 1 year of treatment, the orlistat group lost 6.2kg of initial body weight vs. 4.3kg in the placebo group (P < 0.001). Orlistat treatment plus diet compared with placebo plus diet was associated with significant improvement in glycaemic control, as reflected in decreases in HbA1c (P < 0.001) and fasting plasma glucose (P < 0.001) and in dosage reductions of
oral sulfonylurea medication (P < 0.01). Orlistat therapy also resulted in significantly greater improvements than placebo in several lipid parameters, namely, greater reductions in total cholesterol, (P < 0.001), LDL cholesterol (P < 0.001), triglycerides (P < 0.05), apolipoprotein B (P < 0.001), and the LDL-to-HDL cholesterol ratio (P < 0.001).

Similar weight loss and improved lipid profiles have also been observed in trials of orlistat in diabetics on metformin (Miles et al 2002) and also in diabetic patients receiving insulin (Kelley et al 2002). Orlistat may therefore be a useful adjunctive therapy for obese patients with Type II Diabetes.

**Insulin**

I shall provide an overview of available insulin therapies in the next chapter. Patients with Type II Diabetes who have persistent hyperglycaemia despite diet, weight reduction and exercise are typically started on an oral hypoglycaemic drug. Insulin is usually only added when they have inadequate control despite use of these drugs.

**Pharmacologic Therapy of Blood Glucose – Recommendations**

If the desired level of glycaemic control is not reached after several months of lifestyle intervention, the patient should be started on drug therapy.

A sulphonylurea is the first line choice for those whose weight is normal or only modestly increased. Conversely, markedly obese patients should be started on metformin as a first line agent.

Patients who are underweight, are losing weight or are ketotic should be started on insulin regardless of age. It is important to consider the possibly of Type I Diabetes in this group, as 25% of Type I Diabetics present after the age of 35 (Leslie and Elliott 1994).
Since most of the available agents lower blood glucose by around 20%, patients whose
degree of glycaemic control is more than 20% above their goal will probably require
combination drug therapy. In addition the progressive nature of Type II Diabetes will also
tend to mandate use of combination therapy if glycaemic targets are to be met. Analysis
of UKPDS found that 50% of patients originally controlled with a single drug require the
addition of a second drug after three years; by nine years 75% of patients needed multiple
therapies to achieve the target HbA1c (Turner et al 1999).

The therapeutic options for patients who fail initial therapy with an oral hypoglycaemic
drug are:

- Add a second drug
- Add insulin
- Discontinue the drug and switch to insulin.

There is no consensus about which option is most effective. The role of insulin in this
setting is the basis of the systematic review to follow.

**Metformin plus Sulphonylureas**

This combination may be tried in patients initially treated with a sulphonylurea who
prefer to avoid insulin injections. Hermann et al (1994) evaluated the use of these drugs
alone and in combination. Either drug alone lowered HbA1c by 0.9 to 1.3%. The highest
dose combination achieved a mean fall in Hb1c of 2.2%. Similar results were reported by
the US Multicentre Metformin Study Group (DeFronzo and Goodman 1995).

A subanalysis of UKPDS (UKPDS 34 1998) suggested that the early addition of
metformin to sulphonylurea therapy may increase the risk of diabetes-related death.
These results warrant further study before firm conclusions can be made.

**Metformin plus a Thiazolidinedione**

Patients who fail initial therapy with metformin may benefit from the addition of a
thiazolidinedione. Metformin and thiazolidinediones both increase insulin sensitivity, but
they act in different ways. Fonseca et al (2000) established this to be an efficacious combination as previously stated.

**Thiazolidinedione plus a Sulphonylurea**
This combination may be used in whom metformin is contra-indicated. Kipnes et al (2001) established this to be an efficacious as previously stated.

**Alpha-glucosidase Inhibitors (Acarbose)**
Acarbose can reduce HbA1c slightly in combination with any other from of therapy. Side effects have limited its use. It may be tried in people who have wide swings in blood glucose concentrations after meals.

**Triple Oral Therapy**
In patients not adequately controlled on two oral agents, switching to insulin is probably more effective than adding a third agent. Schwartz et al (2003) studied 188 Type II Diabetics with inadequate control on two oral agents. They were randomly assigned to either the addition of a third agent or to be switched to metformin plus twice-daily insulin. At the end of study (week 24 of therapy), HbA1c and fasting plasma glucose values showed comparable decreases in the two treatment groups. However, a total of 10 of the 98 subjects randomised to triple oral therapy (10.2%) who failed to improve sufficiently were switched to insulin therapy. An additional four subjects dropped out of the oral treatment group due to adverse events felt to be potentially drug related. Furthermore, cost analysis determined that insulin plus metformin (mean cost 3.20 dollars/day) provided efficacy equal to that of a triple oral drug regimen (10.40 dollars/day).

**Insulin Therapy Alone and In Combination With Drug Therapy**
The evidence supporting insulin therapy alone and in combination with oral agents shall be addressed in the systematic review to follow.
REFERENCES


8. UKPDS 33 (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with


European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk).


### Overview of Insulin Therapy

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<td>Mixture of a neutral insulin and a protamine suspension</td>
<td>30 min</td>
<td>2-12</td>
<td>16-18</td>
</tr>
<tr>
<td>Mixtard 30/70</td>
<td></td>
<td>30 min</td>
<td>2-12</td>
<td>24</td>
</tr>
<tr>
<td>Humulin 20/80</td>
<td></td>
<td>30 min</td>
<td>1-9.5</td>
<td>17-19</td>
</tr>
<tr>
<td>Mixtard 20/80</td>
<td></td>
<td>30 min</td>
<td>2-8</td>
<td>24</td>
</tr>
<tr>
<td>Humulin 50/50</td>
<td></td>
<td>30 min</td>
<td>2-12</td>
<td>16-18</td>
</tr>
<tr>
<td>Mixtard 50/50</td>
<td></td>
<td>30 min</td>
<td>4-8</td>
<td>24</td>
</tr>
</tbody>
</table>

*Fig 1 – Available Insulin Preparations*

*Taken from Couper J., Prins J. MJA 2003; 179 (8): 441-447*
Types of Insulin

Insulins can be divided into four categories according to their duration of action:

1. Rapid-Acting Insulin

To produce an insulin preparation with a faster onset and shorter duration than regular insulin, modifications have been made to the insulin molecule to prevent it from forming dimers and other complexes that slow absorption and delay action (Barnet and Owens 1997). Insulin lispro (Humalog) and insulin aspart (NovoRapid) do not self-aggregate in solution as regular insulin does. Insulin lispro differs from human insulin by an amino acid exchange of lysine and proline at positions 28 and 29 (see figure 2). Insulin aspart is created by the substitution of aspartic acid for proline at position 28. These monomeric insulins have an onset of action within 5-15 minutes, peak action at 30-90 minutes and a duration of action of 2-4 hours (Howey et al 1994 and Home et al 1998). The rapid onset of action and short duration makes these agents useful as ‘prandial’ or ‘bolus’ insulin to be injected at mealtimes.

![Fig 2 - Structure of Insulin Lyspro](Taken from Boyages S. MJA 1999; 170: 349-350)

2. Short-Acting Insulin

Regular human insulin has a delay to onset of action of 30-60 minutes, a peak action of 2-4 hours and an duration of action of up to 8 hours when administered subcutaneously. Patients are instructed to inject regular insulin 20-30 minutes prior to meals to match insulin availability and carbohydrate absorption.
3. Intermediate-Acting Insulin
Neutral protamine Hagedorn (isophane insulin; NPH) insulin is slowly absorbed due to the addition of protamine to regular insulin. It has onset of action in 2-4 hours, peak at 4-10 hours and a duration of action of 10-16 hours. Regular insulin bound to zinc, Lente insulin, has a slightly longer effective duration. Lente and NPH are commonly used as twice daily basal insulins. They can also be mixed with soluble insulins, essentially retaining the properties of the two components, although there may be some blunting of the initial effect of soluble insulin component (especially on mixing with protamine zinc insulin). Lispro protamine suspension and aspart protamine crystallised are also available and are functionally equivalent to NPH; however, they are only available as biphasic analogue mixtures.

4. Long-Acting Insulin
Ultralente is a suspension of insulin in the form of a complex obtained by the addition of a suitable zinc salt. It is absorbed slowly in its zinc crystalline form. The new insulin analogue, insulin glargine, is modified human insulin that forms a microprecipitate in the subcutaneous tissue. It is released slowly with a peakless delivery of about 20-24 hours in most patients.

The Insulin Analogues
In the past, the pharmacokinetic characteristics of insulin preparations have been modified by mixing with substances that delay absorption (eg, protamine and zinc) and by varying crystal size. Recombinant DNA technology has now made possible the creation of analogues of human insulin with altered pharmacokinetic characteristics. These analogues allow insulin to be delivered in a fashion that more closely resembles normal physiology.
Rapid-acting analogues

The rapid-acting insulin analogues insulin lispro and insulin aspart have the following advantages:

i) **Reduction of postprandial increases in blood glucose concentration**, because insulin delivery follows the rise in blood glucose after eating more closely. Anderson et al (1997) found that insulin lispro resulted in a significant lowering of one and two hour postprandial blood glucose concentrations (by 1.3 and 2.0mmol/L) compared with regular insulin in a study of 1008 patients with Type I Diabetes.

ii) **Reduced frequency of hypoglycaemia**, because of their shorter duration of action. Consequent reduced need to snack. A meta-analysis in Type I Diabetes showed the rate of severe hypoglycaemia to be 3.1% with insulin lispro compared with 4.4% with regular insulin (p=0.024) (Brunelle et al 1998).

iii) **Increased convenience**, because their very rapid onset of action allows them to be injected immediately before meals or even after eating.

iv) **Rapid onset of action is not blunted by mixing with NPH insulin**, as is that of regular insulin (Joseph et al 1998).

They do however have the following disadvantages:

i) **Their shorter duration of action can lead to preprandial hyperglycaemia** (Torlone et al 1996).

ii) **Low basal serum insulin concentrations may mandate increased doses of intermediate- or long-acting insulin** (Lalli et al 1999).

iii) **Unknown teratogenicity and long-term safety profile**.

iv) **Higher cost**.
Long-acting analogues

Insulin glargine was created by substituting and adding amino acids to the insulin molecule. The yet to be licensed insulin detemir was created by adding a fatty acid chain, which enhances binding to albumin. In contrast to NPH or Lente insulin, the time action profile for insulin has virtually no peak (see figure 3). A flat dose profile with a low peak of action provides more predictable background control than the intermediate-acting insulins, without the unwanted peaks of action around lunchtime and during the night.

Fig 3 – Time-action profile of NPH and insulin glargine

Serum insulin concentrations after subcutaneous injection of 0.4u/kg body weight of insulin glargine or NPH human insulin on 2 different study days in 15 normal subjects. Data from Heinemann L. et al. Diabetes Care 2000; 23:644
Insulin Regimens

Once-daily regimens

For patients with Type II Diabetes who are not controlled by diet and oral hypoglycaemic drugs, the choice is between adding insulin or discontinuing the drugs and treating with insulin alone. In either case, a once-daily dose of intermediate or long-acting insulin may be sufficient.

For patients treated with insulin alone, a once-daily regimen may be effective, although serum insulin concentrations are more stable in patients taking two doses daily, even when the insulin is long-acting ultralente insulin (Holman and Turner 1985). Taylor et al (2000) compared once-daily ultralente insulin with twice-daily NPH insulin in a 6-month crossover study of 79 patients with Type II Diabetes. The NPH regimen was associated with improved glucose control (HbA1c 9.1 vs 9.7%), fewer hypoglycaemic episodes (171 vs 220) and greater patient satisfaction. Poorer glycaemic control in the ultralente group related primarily to higher evening glucose levels.

For combination NPH or ultralente insulin and drug therapy, it is preferable to take insulin at bedtime (Yki-Jarvinen et al 1992). The rationale for this regimen is that, by suppressing hepatic glucose production overnight, the patient starts the day with a lower fasting blood glucose and can retain the convenience of oral therapy during the day while minimising total insulin requirements.

Insulin glargine may represent the best choice for once daily therapy in patients with Type II diabetes. Compared to NPH or ultralente insulin given at bedtime to supplement oral therapy, insulin glargine achieves similar glycaemic control, with less hypoglycaemia and possibly less weight gain (Yki-Jarvinen, Dressler and Ziemen 2000 and Rosenstock et al 2001).

Contrary to NPH and ultralente, insulin glargine may be most appropriately given in the morning in patients on an oral agent. Fritsche et al (2003) found that a morning dose of insulin glargine lowered HbA1c by 1.24%, compared to 0.96% with a bedtime dose, and 0.84% with bedtime NPH, in a study of 695 patients with Type II Diabetes also receiving glimepiride. Nocturnal hypoglycaemia was also less frequent with morning insulin glargine (17%) and bedtime insulin glargine (23%), than with bedtime NPH (38%).
Twice-daily regimens

Twice daily NPH or lente insulin may provide adequate control in patients with Type II Diabetes. If postprandial rises in blood glucose are a concern, then either oral drugs should be continued or a short acting insulin added. This may be achieved with twice daily injection (before breakfast and before dinner) of a biphasic insulin mixture, which results in four peaks of insulin action (see figure 4).

![Figure 4 - Effect of twice-daily biphasic insulin regimen](http://www.uptodate.com)

In practice, when insulins are mixed the peaks of the individual profiles tend to merge somewhat. This effect is most prominent with zinc-containing insulin preparations such as lente or ultralente insulin (Colagiuri and Villalobos 1986). Because of variability in peak effect, it may be more difficult to achieve excellent glycaemic control with premixed insulins. The morning dose of intermediate-acting insulin may not be sufficient to prevent a post-lunchtime rise in blood sugar. Similarly, the intermediate-acting insulin administered before the evening meal may not be sufficient to achieve an acceptable fasting blood sugar the next morning unless a larger dose is given, which increases the risk of nocturnal hypoglycaemia. Thus, if near normoglycaemia is the goal it may be preferable to keep basal insulins separate from pre-meal insulins to enable them to be adjusted independently.
**Basal-bolus regimen**

Due to the limitations of twice daily biphasic insulin injections highlighted above, a proportion of people will require conversion to a 3-4 injections daily regimen. For intensive therapy we must aspire to mirror a physiological insulin secretion profile – this can only be achieved with a regime consisting of an intermediate- or long-acting insulin to provide a basal rate and then bolus/pre-meal injections of rapid- or short-acting insulin. It is preferable to give the intermediate- or long-acting insulin into a site (leg or buttock) where absorption is slow and the pre-meal bolus into the abdomen from which insulin is absorbed more rapidly.

**Continuous subcutaneous insulin infusion (insulin pump)**

Continuous subcutaneous insulin therapy has been used successfully in both research studies like the DCCT (1993) and in large clinical practices (Mecklenburg et al 1985). Only fast-acting insulin (regular, or monomeric analogues like lispro and aspart) is used with continuous therapy. The background insulin is supplied in the form of a basal infusion (comprising about 60 percent of the total daily dose) with pre-meal bolus doses given to minimize postprandial hyperglycaemia. Patients with Type II Diabetes may be considered for pump use if they experience severe hypoglycaemia and wide fluctuations of glucose levels.

Insulin pump therapy may achieve slightly better glycaemic control than multiple daily injections and reduces hypoglycaemic events (Pickup, Mattock, Kerry 2002). There are, however, disadvantages to continuous therapy. The costs of the pump and supplies are higher than those of ordinary syringes and needles. Many patients who use pumps also complain that the treatment is awkward, uncomfortable, embarrassing, or unpleasant. Voluntary termination of this pump therapy is common, occurring in one study in 29 percent of 177 patients within five years (Guinn, Bailey and Mecklenburg 1988).

**Summary**

There is currently no consensus as to which insulin formulations or what regimen to use in Type II Diabetes. There is also uncertainty as to how to most appropriately combine insulin therapy with oral drugs. In the systematic review to follow I have endeavoured to ascertain just what evidence exists supporting the use of various formulations and regimens, what are the potential advantages and disadvantages, and what is the most appropriate way of combining insulin therapy with oral therapy.
REFERENCES


Systematic Review Research Protocol

The Question

The purpose of this dissertation is to address one fundamental question:

"How should we best use insulin in the management of Type II Diabetes?"

In reality, in answering this question I am called upon to address a multitude of subsidiary questions including the following?

"When should insulin be used in Type II Diabetes?"
"What different formulations are available?"
"What are we hoping to achieve with insulin therapy?"
"What regimen is most effective in achieving this aim?"
"What are the advantages/disadvantages of each formulation/regimen?"
"What are the risks of insulin therapy?"
"Should insulin be used alone or in combination with oral drug therapy?"

The study factor ‘insulin’ is not a single agent, but a number of different formulations that can be used in a number of different combinations (or regimens). This adds a significant increased complexity to the question, as it necessitates the comparison of multiple different treatment regimens.

The study population is fairly clearly defined, that being Type II Diabetes. That said, diagnostic criteria do vary slightly between different countries and have evolved somewhat with the passage of time. There will also be significant differences between the overall levels of glycaemic control among subjects in different studies, which may pose difficulties in interpretation. i.e. One study may examine subjects with a pre-treatment median HbA1c of 12% while another study may have a median HbA1c of 8% - one would imagine each population may respond differently to the same treatment/intervention.
The most important outcomes in assessing a treatment in Type II Diabetes are rates of complications (microvascular and macrovascular) and mortality data. However, due to the long-term nature of these outcomes, most studies are of too short duration to demonstrate statistically significant differences. In Chapter 2, I detailed the evidence supporting normoglycaemia as a therapeutic target. With this in mind, I shall look at HbA1c and fasting blood glucose levels as surrogate markers of improved glycaemic control, accepting that it is now well established that improved glycaemic control is associated with better outcomes. It is also established that tighter glycaemic control increases the risk of hypoglycaemic events, so this will also be an important endpoint of interest. Insulin therapy is also frequently associate with weight gain, so where reported I shall also collate data on weight changes with different therapies.

Finding Relevant Studies
Finding all the relevant studies is not easy. There are currently over 22000 journals in the biomedical literature and MEDLINE indexes only 3700 of these (NHMRC 2000). To maximise my data capture I shall employ the following strategies:

- literature search in MEDLINE from 1966 to December 2003 (see Appendix 1)
- literature search in EMBASE from 1980 to December 2003 (see Appendix 2)
- letter writing to the UK and Australian divisions of the three key pharmaceutical companies involved in insulin therapy requesting unpublished data (see Appendix 7 and Appendix 8)
- bibliographical searching for papers missed by the above strategies

Because of their unique ability to control for confounders, known or unknown, randomised controlled trials (RCT's) generally provide the best evidence of efficacy for interventions. I shall therefore restrict my literature search to RCT's. Previous systematic reviews shall also be evaluated to ensure I have not missed any important trials with my search strategy.
Study Selection

I shall execute the MEDLINE and EMBASE searches as detailed in Appendices 1 and 2. Due to my limitations with respect to accessing translations, I shall limit my search to only English language papers. I shall also include only those studies with an abstract available on the OVID – NHS KA24 site that serves as my access to MEDLINE and EMBASE.

I shall then peruse the abstracts of studies yielded by the above searches and select all those studies that meet the following inclusion criteria:

- Subjects with Type II Diabetes
- Random treatment allocation
- Involves use of insulin (alone or in combination with oral hypoglycaemic drugs)
- Minimum of 4 weeks treatment duration
- Minimum of 10 patients in each arm
- Reports glucose measurements or HbA1c AND rates of hypoglycaemia

I shall tabulate the reason for exclusion of studies yielded by the literature search but not included in further analysis according to the following criteria:

1. Not a randomised controlled trial
2. Study outcomes don’t match
3. Wrong patient group
4. Insufficient patient numbers
5. Inadequate study duration
6. Duplicate study
7. Irrelevant treatment comparison (includes unlicensed treatments)

I will then endeavour to access full-text versions of all the included studies using the following sources:

- OVID – NHS KA24 site
Studies not available from one of the above sources will be excluded from further analysis.

I shall conduct a further bibliographical search of the eligible studies available in full text looking for any relevant studies my searches may have missed.

Additional eligible studies may become available from my written request to the key pharmaceutical companies (see Appendices 3 and 4). These studies shall be subject to the same inclusion criteria as the others.

**Anticipated Difficulties**

Despite employing the strategies above, there may still be an inadequate evidence base to allow reliable conclusions to be drawn; The National Institute of Clinical Excellence (NICE 2002) asserts:

\[
\text{"There is no direct evidence to support the use/choice of any one insulin type or regime over another"}
\]

\[
\text{"Local experience, patient preference and relative costs should inform the choice of insulin type and regimen as there is little research evidence in this area"}
\]

I am hopeful that new data may have emerged since NICE conducted their review. Furthermore, I suspect their interpretation of the evidence may differ from my own, particularly as they may be influenced by the funding implications of their conclusions.
Critical Appraisal – Assessment of Study Quality

“Quality assessment of individual studies that are summarised in systematic reviews is necessary to limit bias in conducting the systematic review, gain insight into potential comparisons, and guide interpretation of findings” (Cochrane Reviewers’ Handbook 4.2.0)

Numerous quality assessment methods have been utilised but the optimal use of quality items and scales is still not clear (Moher et al 1995). Because there is no ‘gold standard’ for the true validity of a trial, it is difficult to validate any proposed scoring system. Cochrane advises that none of the currently available scales can be recommended without reservation and that “it is preferable to use simple approaches for assessing validity that can be fully reported” (Cochrane Reviewer’s Handbook 4.2.0). Guidance from NHMRC (2000) recommends that items be restricted generally to those that have been shown to affect the results of trials. For these reasons I have elected to adopt the following quality appraisal checklist (taken from NHMRC 2000):

1. **Method of treatment assignment**
   a. Correct, blinded randomisation method described
      OR randomised, double-blind method stated
      AND group similarity documented
   b. Blinding and randomisation stated but method not described
      OR suspect technique
   c. Randomisation claimed but not described and investigator not blinded
   d. Randomisation not mentioned

2. **Control of selection bias after treatment assignment**
   a. Intention to treat analysis AND full follow-up
   b. Intention to treat analysis AND <15% loss to follow-up
   c. Analysis by treatment received only OR no mention of withdrawals
   d. Analysis by treatment received AND no mention of withdrawals
      OR >15% withdrawals/loss to follow-up/post-randomisation exclusions
Blinding

e. Blinding of outcome assessor
   AND patient and care-giver
f. Blinding of outcome assessor
   OR patient and care-giver
g. Blinding not done

3. Outcome assessment (if blinding was not possible)
   a. All patients had standardised assessment
   b. No standardised assessment or not mentioned

Data Synthesis

The complexity of comparing multiple treatment regimens poses challenges in terms of data synthesis. The desire to ‘pool data’, where appropriate, must be offset against apparently small differences in treatment regimens or study populations that may have large impacts on outcomes. It is my expectation that it will be difficult to synthesise the data in a quantitative fashion. I will critically appraise the available evidence and synthesise the findings qualitatively. This methodology is supported by guidelines from the National Health and Medical research Council guidelines (NHMRC 2000), which state that quantitative synthesis of the data “is neither necessary nor sufficient to make a review systematic.” However, wherever possible, I will also quantitatively synthesise data the mean change in HbA1c and weight changes as these are fairly consistently reported across trials.
Data from the publications will be compiled in table form as this will facilitate my grouping and understanding of the evidence. Trials evaluating similar treatment regimens or agents will be grouped together to allow results to be compared more readily. Data from the tables will then be synthesised in order to make specific evidenced based recommendations about the various regimens.
REFERENCES


Literature search results

The following flow diagram gives an overview of the yield of the literature search and eligible studies.

Further details of the search methodology, yield and complete lists of eligible studies are presented as appendices to this dissertation as follows:

- Appendix 1: Medline search string
- Appendix 2: Embase search string
- Appendix 3: Medline eligible studies after title and abstract review
- Appendix 4: Medline excluded studies after title and abstract review
- Appendix 5: Embase eligible studies after title and abstract review
- Appendix 6: Embase excluded studies after title and abstract review
- Appendix 7: Letter requesting unpublished data
- Appendix 8: List of pharmaceutical companies approached for unpublished data
- Appendix 9: Final list of eligible studies after quality appraisal inclusive of additional eligible studies identified by bibliographical search and written requests to key pharmaceutical companies
Flow of eligible studies

177 studies identified by Medline search

57 studies eligible after title & abstract review

186 studies identified by Embase search

18 studies eligible after title & abstract review (large exclusion due to duplication)

20 studies identified by bibliographical search & request to pharma

95 studies eligible for quality appraisal of full publication

88 studies included in final analysis of the evidence
Quality Assessment of Included Studies

As per my research protocol I have undertaken a quality assessment of each included study using the following quality appraisal checklist (NHMRC 2000)\(^1\):

1. **Method of treatment assignment**
   a. Correct, blinded randomisation method described
      OR randomised, double-blind method stated
      AND group similarity documented
   b. Blinding and randomisation stated but method not described
      OR suspect technique
   c. Randomisation claimed but not described and investigator not blinded
   d. Randomisation not mentioned

2. **Control of selection bias after treatment assignment**
   a. Intention to treat analysis AND full follow-up
   b. Intention to treat analysis AND <15% loss to follow-up
   c. Analysis by treatment received only OR no mention of withdrawals
   d. Analysis by treatment received AND no mention of withdrawals
      OR >15% withdrawals/loss to follow-up/post-randomisation exclusions

3. **Blinding**
   a. Blinding of outcome assessor
      AND patient and care-giver
   b. Blinding of outcome assessor
      OR patient and care-giver
   c. Blinding not done

4. **Outcome assessment (if blinding was not possible)**
   a. All patients had standardised assessment
   b. No standardised assessment or not mentioned
<table>
<thead>
<tr>
<th>Study</th>
<th>Method of treatment assignment</th>
<th>Control of selection bias after treatment assignment</th>
<th>Blinding</th>
<th>Outcome assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 - HOE 901/2004 Study Investigators Group (2003)</td>
<td>A Double-blind randomisation via telephone</td>
<td>D ITT analysis but 25% drop outs</td>
<td>C Insulin glargine (clear solution) vs NPH (cloudy solution)</td>
<td>A</td>
</tr>
<tr>
<td>M2 - Wulffele et al (2002)</td>
<td>B Double-blind randomisation stated but slightly older metformin group</td>
<td>B ITT analysis with 10% drop outs</td>
<td>A Insulin plus metformin vs Insulin plus matched placebo</td>
<td>A</td>
</tr>
<tr>
<td>M3 - Herz et al (2003)</td>
<td>A Randomisation stated and crossover design and groups comparable</td>
<td>D ITT analysis (1 dose required) but 16% drop outs</td>
<td>C Open-label comparison of Humalog Mix 25 and Mixtard 30/70</td>
<td>A</td>
</tr>
<tr>
<td>M4 - Strowig et al (2002)</td>
<td>A Random assignment with sealed sequentially marked envelopes</td>
<td>C Analysis by treatment received (88/92)</td>
<td>C Insulin +/- metformin or troglitazone</td>
<td>A</td>
</tr>
<tr>
<td>M5 - Herz et al (2002)</td>
<td>A Randomisation stated and crossover design</td>
<td>B ITT analysis with 10% drop outs</td>
<td>C Open-label comparison of insulin 30/70 and lispro Mix25</td>
<td>A</td>
</tr>
<tr>
<td>M6 - UKPDS 33 (1998)</td>
<td>A Random assignment with centrally produced, computer generated allocations in sealed opaque envelopes.</td>
<td>B ITT analysis with 4.4% drop outs</td>
<td>C Unblinded comparison of multiple different therapies</td>
<td>A</td>
</tr>
<tr>
<td>M7 - UKPDS 49</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>A</td>
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<td>Study (Year)</td>
<td>Randomisation Method</td>
<td>ITT Analysis</td>
<td>Therapies Compared</td>
<td>Notes</td>
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<tr>
<td>(1999)</td>
<td>Random assignment with centrally produced, computer generated allocations in sealed opaque envelopes</td>
<td>ITT analysis with 4.4% drop outs</td>
<td>Unblinded comparison of multiple different therapies</td>
<td></td>
</tr>
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<td>M8 - Schwartz et al (1998)</td>
<td>Double-blind randomisation stated and groups comparable</td>
<td>ITT analysis (1 dose and 1 follow-up visit required) with 10% drop outs</td>
<td>Placebo vs troglitazone 200mg or 600mg (single-blind placebo run-in)</td>
<td>A</td>
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<td>M9 - Raskin et al (2001)</td>
<td>Randomisation codes generated with “an internal software system” and groups comparable</td>
<td>ITT analysis (required one postbaseline measurement) but 20% drop outs</td>
<td>Placebo vs rosiglitazone 2mg bd or 4mg bd (single-blind placebo run-in)</td>
<td>A</td>
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<tr>
<td>M10 - Rosenstock et al (2001)</td>
<td>Randomisation claimed, but not described. Groups seem comparable</td>
<td>ITT analysis (required one postbaseline measurement) with 10% drop outs</td>
<td>Insulin glargine (clear solution) vs NPH (cloudy solution)</td>
<td>A</td>
</tr>
<tr>
<td>M11 - HOE 901/3002 Study Group (2000)</td>
<td>Randomisation via telephone to an independent agency</td>
<td>ITT analysis with 14% drop outs</td>
<td>Insulin glargine (clear solution) vs NPH (cloudy solution)</td>
<td>A</td>
</tr>
<tr>
<td>M12 - Boehm et al (2002)</td>
<td>Randomisation claimed but not described. Groups seem comparable</td>
<td>ITT analysis (required drug exposure plus any efficacy data) with 8% drop outs</td>
<td>Insulin 30/70 30mins pre-meal vs. Insulin aspart 30 10mins pre-meal</td>
<td>A</td>
</tr>
<tr>
<td>M13 - Zargar et al (2002)</td>
<td>Randomisation by consecutive allocation to one</td>
<td>Analysis by treatment received with</td>
<td>i) Twice daily insulin regimen alone ii) Twice daily insulin +</td>
<td>A</td>
</tr>
<tr>
<td>Study</td>
<td>Notes</td>
<td>Randomisation</td>
<td>ITT Analysis</td>
<td>Comparator</td>
</tr>
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<td>M16 – Hermann et al (2001)</td>
<td>A</td>
<td>Double-blind randomisation performed by centre in blocks of four and groups comparable</td>
<td>B</td>
<td>Insulin plus metformin vs Insulin plus matched placebo</td>
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<td>Selection of Patients</td>
<td>Randomisation and Group Similarity</td>
<td>Metformin and Full Follow-up</td>
<td>Analysis by Treatment Received</td>
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<td>M20 – Guvenen and Gedik (1999)</td>
<td>C</td>
<td>Double-blind randomisation and groups comparable</td>
<td>A</td>
<td>B</td>
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<tr>
<td>M21 – Aviles-Santa et al (1999)</td>
<td>A</td>
<td>Double-blind randomisation stated and groups comparable</td>
<td>B</td>
<td>ITT analysis (required one post-baseline HbA1c measurement) with 7% post-randomisation drop outs</td>
</tr>
<tr>
<td>M22 – Standl et al (1999)</td>
<td>A</td>
<td>Double-blind randomisation stated and groups comparable</td>
<td>C</td>
<td>Analysis by treatment received only with 10% excluded from efficacy analysis</td>
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<tr>
<td>M23 – Abraira et al (1998)</td>
<td>A</td>
<td>Blinded randomisation and group similarity documented in other papers</td>
<td>B</td>
<td>ITT analysis with 8% drop outs</td>
</tr>
<tr>
<td>M24 – Relimpio et al (1998)</td>
<td>A</td>
<td>Randomisation claimed but not described. Groups seem comparable</td>
<td>D</td>
<td>Analysis by treatment received and 22% drop-outs</td>
</tr>
<tr>
<td>M25 – Niazi and Muzaffar (1998)</td>
<td>C</td>
<td>Selection of patients was ‘at random’ and they were</td>
<td>D</td>
<td>Basis of analysis is unclear and 50% of the</td>
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<tr>
<td>Study Reference</td>
<td>Randomisation</td>
<td>Analysis</td>
<td>Treatment</td>
<td>Outcome</td>
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<td>M26 - Tovi et al (1998)</td>
<td>A Randomisation using a 'random-number table'</td>
<td>C Analysis by treatment received only with 12.5% excluded from analysis</td>
<td>C Insulin vs continued sulphonylurea in patients with secondary oral failure</td>
<td>A</td>
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<tr>
<td>M27 - Buse et al (1998)</td>
<td>A Double-blind randomisation stated and groups comparable</td>
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<td>C Unblinded - Insulin +/- Glibenclamide (should have used GB placebo!)</td>
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<td>M32 - Calle-Pascual et al (1995)</td>
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<td>A/C No reported drop-outs with suggested ITT</td>
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sequentially into three groups – suspect technique.

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<td>A Double-blind randomisation stated and groups comparable</td>
<td>Analysis by treatment received with 5% drop outs</td>
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<td>M45 - Lewitt et al</td>
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<td>M47 - Casner</td>
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<td>“Block-randomisation”</td>
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<td>(1988)</td>
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<td>M48 - Lins et al</td>
<td>B</td>
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<td>(1988)</td>
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<td>M57 - Groop et al (1984)</td>
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<td>Randomisation claimed but not described. Groups seem comparable</td>
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<td>ITT analysis (required 1 post-baseline HbA1c) with 9% drop outs</td>
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<td>Open-label comparison of bedtime NPH plus glimepiride vs NPH twice daily vs Mix 30/70 bd</td>
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<td>Analysis by treatment received with 26% post randomisation exclusions</td>
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<td>Randomisation claimed but not described. Groups seem comparable</td>
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<td>No reported drop-outs with suggested ITT analysis (not explicit)</td>
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<td>E11 – Anderson et al (1997)</td>
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<td>No reported drop-outs with suggested ITT analysis (not explicit)</td>
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<td>A Randomisation stated and cross-over design. Groups seem comparable</td>
<td>B Analysis by treatment received with 18% drop outs</td>
<td>C Twice-daily NPH vs once-daily ultralente</td>
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<tr>
<td>B7</td>
<td>Wolffenbuttel et al (1996)</td>
<td>A Randomisation claimed but not described. Groups seem comparable</td>
<td>B ITT analysis with 7% drop outs</td>
<td>C Mixtard 30/70 bd vs bedtime-NPH + glibenclamide vs morning-NPH + glibenclamide.</td>
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<td>B8</td>
<td>Yki-Jarvinen et al (1999)</td>
<td>A Randomisation into four groups using minimisation of differences for specified variables</td>
<td>C Analysis by treatment received with 8% drop outs</td>
<td>C Bedtime NPH plus: i) breakfast NPH or ii) Glyburide plus placebo-metformin or iii) Metformin plus placebo-glyburide or iv) metformin plus glyburide</td>
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<td>B9</td>
<td>Basty et al (1999)</td>
<td>A Randomisation</td>
<td>B ITT analysis</td>
<td>C Sulphonylurea plus</td>
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| **B10 – UKPDS 34**  
(1998) |   |   |   |
| A | Random assignment with centrally produced, computer generated allocations in sealed opaque envelopes. | B | ITT analysis with 4% drop outs |
|   |   | C | Unblinded comparison of multiple different therapies |
|   | with 6% drop outs | preprandial insulin lispro vs Sulphonylurea plus bedtime-NPH vs bedtime-NPH plus preprandial insulin lispro |
|   |   |   | A |

| **B11 – Roach et al**  
(1999) |   |   |   |
| A | Randomisation stated and cross-over design. Groups seem comparable | A | ITT analysis and full follow-up |
|   |   | C | Humalog Mix50 pre-breakfast plus Mix25 pre-dinner vs human insulin 50/50 pre-breakfast plus 30/70 pre-dinner |
|   |   |   | A |

| **B12 – Roach, Yue and Arora**  
(1999) |   |   |   |
| A | Randomisation stated and cross-over design. Groups seem comparable | B | ITT analysis with 10% drop outs |
|   |   | C | Humalog Mix25 bd vs human insulin 30/70 bd |
|   |   |   | A |

| **B13 – Riddle et al**  
(2003) |   |   |   |
| A | Randomisation in the order which subjects qualified using a centralised telephone system | B | ITT analysis with 9% drop outs |
|   |   | C | Insulin glargine (clear solution) vs human NPH (cloudy solution) at bedtime |
|   |   |   | A |

| **B14 – UKPDS 57**  
(2002) |   |   |   |
<p>| A | Random assignment with centrally produced, computer generated allocations in sealed opaque envelopes. | B | ITT analysis with 4% drop outs |
|   |   | C | Diet vs insulin vs sulphonylurea + insulin |
|   |   |   | A |</p>
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<th>Treatment Comparison</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>B15 - Davies et al (2005)</td>
<td>Randomisation claimed but not described. Groups seem comparable</td>
<td>ITT (ΔPP) analysis with 9% drop outs</td>
<td>Patient-lead vs clinician-lead insulin glargine titration algorithm – blinding not possible</td>
<td>A</td>
</tr>
<tr>
<td>B16 - Janka et al (2005)</td>
<td>Random assignment stratified by centre with centrally produced, computer generated allocations</td>
<td>ITT analysis with 9% drop outs</td>
<td>Glargine + glimepiride + metformin vs Mixtard 30/70 twice daily</td>
<td>A</td>
</tr>
<tr>
<td>B17 - Raskin et al (2005)</td>
<td>Stratified randomisation using lowest number available to each site. Groups seem comparable</td>
<td>ITT analysis with 10% drop outs</td>
<td>Biasp70/30 twice daily +/- OHA vs insulin glargine +/- OHAs</td>
<td>A</td>
</tr>
<tr>
<td>B18 - Malone et al (2003)</td>
<td>Stratified randomisation stated, not described. Groups seem comparable</td>
<td>ITT analysis with 9% drop outs</td>
<td>Mix25 + metformin vs glibenclamide + metformin</td>
<td>A</td>
</tr>
<tr>
<td>B19 - Kilo et al (2003)</td>
<td>Randomisation claimed but not described. Groups seem comparable</td>
<td>ITT analysis with 6% drop outs</td>
<td>BiAsp30 od + metformin vs bedtime NPH + metformin vs Mixtard 30/70 od + metformin</td>
<td>A</td>
</tr>
<tr>
<td>B20 - Christiansen et al (2003)</td>
<td>Randomisation claimed but not described. Groups seem comparable</td>
<td>ITT analysis with 3% drop outs</td>
<td>BiAsp30 twice daily vs NPH twice daily</td>
<td>A</td>
</tr>
</tbody>
</table>
Quality Appraisal Conclusions

95 articles were identified as eligible for inclusion after title and abstract review. Seven of these studies were excluded after quality appraisal of the full publication for the reasons as stated in the table above.

After critical review of all eligible studies I have made the following general observations and conclusions:

- There are a large number of single centre, small trials with a limited number of patients
- Methodology and quality have improved with the passage of time
- Glycaemic targets have become more aggressive over the last few decades and this is reflected in study designs. Many of the patients in the older trials would not even be eligible for inclusion in more recent trial due to their very poor glycaemic control.
- Some of the conclusions of the smaller, older trials are questionable due to methodological concerns or significant differences caused by the evolution of clinical practice.
- Reductions in HbA1c become increasingly difficult to achieve as the glycaemic targets become lower. This poses particular challenges for newer agents in terms of demonstrating both a clinically and statistically significant difference to existing treatments. Trials evaluating the newer agents are generally appreciably larger in order to obtain adequate statistical power to demonstrate small differences between treatments
- Large scale trials and those published in well-recognised, peer-reviewed journals are of higher quality
- Loss to follow-up and drop-outs increase with the duration of the study and the complexity of study visits. Many of the older, smaller studies claim complete follow-up/retention of enrolled patients. It seems likely that some investigators may simply exclude patients who are lost to follow-up from the discussion and final analysis.
- Where studies do not comment on withdrawals or loss to follow-up, it is difficult to know if there were any. It is not safe to assume that no comment means no withdrawals even in short-term, small studies
- The majority of the studies are not blinded, most likely due to difficulties inherent in requiring patients to undergo placebo subcutaneous injections
- The potential bias introduced by lack of blinding is partially offset by the fact that most of the trials have a ‘hard endpoint’ of HbA1c. However the lack of blinding may still allow a systematic bias to be introduced by virtue of other changes to the patients management that may influence their glycaemic control
- All trials had some form of standardised assessment of glycaemic control, most commonly HbA1c and FPG. As newer agents, such as the rapid-acting insulin analogues often struggle to demonstrate significant superiority on these traditional outcomes, other parameters such as post-prandial glucose or glycaemic excursion are increasingly being evaluated and presented
• The method of randomisation is frequently described very poorly. Some studies that claim ‘randomisation’ use highly questionable techniques and these are sometimes reflected in significantly unbalanced groups at baseline. Conversely, it is truly remarkable to see how similar randomised groups are at baseline in the large, well randomised studies.

• The nature of the final analysis i.e. ITT, per-protocol or treatment received is frequently not explicitly stated, especially with older studies. There is no consensus in the literature as to what is acceptable to define as ITT analysis. Most studies do not include all randomised patients, but rather prefer to base it on all randomised patients who receive at least one dose of study drug.

Insulin regimens vs OHAs (n=22)

A total of 22 studies that performed a randomised comparison of insulin vs oral hypoglycaemic agents were eligible for final analysis.

UKPDS studies (n=4)
The biggest source of data comparing insulin to OHAs comes from the UK Prospective Diabetes Study Group and I have included data from 4 separate UKPDS publications (UKPDS 33 (1998), 34 (1998), 49 (1999) and 57 (2002)) as they each include different findings of relevance. The most important finding of the UKPDS study was that it established the benefits of intensive treatment of type 2 diabetes with impressive reductions in microvascular endpoints. Prior to UKPDS, some clinicians felt that tight glycaemic control was not important in type 2 diabetes and simply focused on avoidance of symptoms of hyperglycaemia. An addition finding of importance, presented in UKPDS 49 (2002) is the observation that there is a progressive deterioration of diabetes control such that the majority of patients with type 2 diabetes will ultimately require multiple therapies.

In terms of glycaemic control in non-obese patients with recently diagnosed type 2 diabetes, no agent stood out within the different intensive control groups (UKPDS 33 (1998)). A greater proportion of patients assigned to insulin had achieved a FPG<7.8mmol/L after 9 years follow-up, but this did not translate into improved HbA1c. Overall, oral agents were associated with less weight gain and a lower rate of hypoglycaemia than insulin therapy. On this basis, it would seem reasonable to prefer the use of oral agents initially and reserve insulin for patients with inadequate control on oral therapy.

In obese type 2 diabetics, UKPDS 34 (1998) data would suggest that metformin should be considered the agent of choice for first line drug therapy. It achieved similar glycaemic control to the other intensive therapy groups, but achieved a significantly greater reduction in ‘any diabetes related endpoint’ and a greater reduction in all-cause mortality. Metformin was also the only agent to achieve a statistically significant reduction in the risk of macrovascular disease (RRR 30% p=0.020). Addition of metformin to sulfonylurea was associated with a surprising, significant
increase in the risk of diabetes related death. It is very difficult to know how to interpret this finding in the context of the favourable findings for metformin when used first line. I feel that the finding of increased mortality when metformin is added to sulfonylurea may represent extreme play of chance as it is based on relatively low number of outcomes. Overall, the data suggests that metformin should be the preferred agent of choice for first line use in obese type 2 diabetics.

**Studies comparing continued oral therapy to initiation of insulin (n=8)**

There were eight eligible studies that compared continuation of oral therapy to initiation of insulin therapy.


Initiation of insulin therapy in the context of secondary oral failure consistently improved glycaemic control with a mean decrease in HbA1c of 1.96% (range: -1 to -4.9). Factors which influence the degree of improvement in HbA1c may include the study duration, the glycaemic targets specified by the study protocol and the degree of glycaemic control at the study's outset. Weight gain is a consistent finding upon initiation of insulin therapy with a mean weight gain of 2.75kg (range +0.8 to +6kg). Likewise, the rate of hypoglycaemia increases upon initiation of insulin and tighter glycaemic control is associated with an increased risk of hypoglycaemia. Overall, these data demonstrate clear benefits of initiating insulin in patients with secondary oral failure, at a cost of moderate weight gain and increased risk of hypoglycaemia.

The choice of insulin therapy and whether or not to combine with oral therapy will be discussed in detail when the relevant studies are reviewed in a later section. It is however worth paying particular attention to the study by Yki-Jarvinen (1992), as it performed a very useful comparison between five different therapeutic regimens commonly used in patients with secondary oral failure. In this study, insulin therapy
reduced HbA1c by an average of 1.75% after 3 months. Multiple insulin injection regimens (Mixtard 30/70 or basal bolus regimen) were no more effective than a simpler regimen of NPH once daily in combination with oral agents. The best insulin regimen based on best glycaemic control, least weight gain and less hyperinsulinaemia was bedtime NPH with continued OHAs.

Another important observation made by Herz M et al (2002) was the fact that Humalog Mix25 offered the convenience of post-prandial dosing (<15mins) without compromise to glycaemic control when compared to Humalog Mix25 given immediately pre-prandially.

Data from Alvarsson M et al (2003) and Roach P et al (2001) also suggest that insulin can be initiated without significantly compromising the patients quality of life or treatment satisfaction.

Studies comparing addition of a second oral agent to the initiation of insulin (n=10)
A total of ten eligible studies were identified which compared the addition of a second oral agent to the initiation of insulin in patients with secondary oral failure. The addition of a second oral agent consistently improved glycaemic control to a similar extent as the initiation of insulin.


In these eight studies the addition of metformin reduced HbA1c by an impressive mean of 2.35% (range -1.1 to -5). This compared to a remarkable similar mean reduction of 2.25% (range -1.5 to -4.1) with insulin based regimens. Patients randomised to the addition of metformin lost a mean of 0.4kg (range -1.2kg to +0.4kg) whereas patients receiving insulin consistently gained weight, with a mean
gain of 2.3kg (range +0.8 to +4.1). On the basis of these eight studies, the addition of a second oral agent should be preferred to the early initiation of insulin.

One study (Fanghanel et al 1996) evaluated metformin alone vs insulin alone in patients with secondary sulfonylurea failure. Both treatments achieved similar impressive reductions in HbA1c of approx. 4%, but metformin had other significant benefits on weight loss, blood pressure and lipids that may help explain the apparent impact of metformin on macrovascular disease observed in UKPDS.

The study by Schwartz et al (2003) evaluated triple oral therapy (secretagogue, metformin + glitazone) vs Novolin 70/30 bd + metformin in patients with inadequate glycaemic control on two oral agents. In this study both treatments achieved a similar improvement in HbA1c of approx 2% and similar weight gain. Triple oral therapy was more expensive than initiation of insulin, but either regimen would seem a reasonable option based on these results.
Comparison of different insulin regimens (n=31)

A total of 31 of the eligible studies evaluated different insulin regimens, either alone or where randomised groups received the same oral therapy. The number of different regimens compared in these studies highlights the large number of different options available to patients and clinicians. Many of the studies demonstrate similar glycaemic control and so other therapy related issues such as weight gain, frequency of hypoglycaemia or complexity of regimen assume increased importance.

To aid in the interpretation of these studies I have grouped them based on trials which make similar randomised comparisons.

Comparison of insulin glargine and NPH (n=6)

Six studies were identified evaluating insulin glargine in type 2 diabetes.

Five of these compared insulin glargine to NPH, which is currently the most common used basal insulin (HOE 901/2004 Study Investigators Group (2003), Rosenstock et al (2001), Yki-Jarvinen H et al (2000), The HOE 901/3002 Study Group, Fritsche A et al (2003), and Riddle M et al (2003)).

In these five studies, both glargine and NPH lead to similar significant improvements in glycaemic control. HbA1c was reduced by a mean of 1.01% on insulin glargine (range -0.41 to 1.65%). HbA1c was reduced by a mean of 0.92% on NPH (range -0.59 to -1.59%).

The study by Fritsche et al (2003) found that morning insulin glargine provided better glycaemic control than either bedtime glargine or bedtime NPH, but it is difficult to know how to interpret this isolated finding.

Differences in reporting and classification of hypoglycaemia between trials make it difficult to pool the data, but there is a consistent finding of fewer nocturnal hypoglycaemic episodes on insulin glargine compared to NPH. It is possible that in ‘real-world’ clinical practice the higher rate of hypoglycaemia with NPH may lead to
inferior glycaemic control as patients may end up reducing their insulin dose due to fear of recurrent hypoglycaemia, however this remains unproven.

One study Davies et al. (2005) compared a patient lead glargine titration algorithm to a physician lead titration algorithm. It found that the patient-lead algorithm achieved marginally better glycaemic control at the expense of a small increase in the rate of hypoglycaemia.

Based on its superior pharmacokinetic profile and reduced risk of nocturnal hypoglycaemia, it would seem reasonable to prefer insulin glargine to NPH as the basal insulin of choice, particularly in patients who have problems with nocturnal hypoglycaemia on NPH.

Comparisons between different basal insulins (not including NPH vs glargine) (n=4)

Four other studies primarily addressed the choice between the other (non-glargine) basal insulins (Holman et al (1987), Tindall et al (1988), Stehouwer et al (2003) and Taylor et al (2000)).

The small cross-over study by Holman et al (1987) suggested that basal insulin (Ultralente), alone or in combination with a sulfonylurea, were preferable to the addition of metformin in patients with inadequate glycaemic control on maximal dose sulfonylurea.

Tindall et al (1988) demonstrated improved glycaemic control with the use of a basal insulin in patients with secondary oral failure. They found Neulente insulin to be preferable to Humulin-Zn due to the high rate of nocturnal hypoglycaemia with Humulin-Zn.

Stehouwer et al (2003) demonstrated that twice daily insulin (NPH or Mixtard) is superior to bedtime NPH + glimepiride in obese patients with secondary oral failure.
The study by Taylor et al (2000) also supports the use of NPH twice daily, as it achieved superior glycaemic control to Ultralente once daily, with significantly greater reductions in HbA1c and fewer hypos.

**Comparison of synthetic vs human combinations of intermediate and short acting insulin twice daily (n=7)**


These studies have all been published since 1999 as part of the development program for the newer rapid-acting insulin analogues insulin lispro (n=6) and insulin aspart (n=1). They have compared these newer analogues to human insulin. It is prudent to consider the sponsorship of the studies and affiliation of the authors when considering the validity of the conclusions presented in the publications. I feel that the authors tend towards overstating the value of the newer agents.

None of the studies demonstrated the newer insulin analogues to achieve superior glycaemic control as assessed by HbA1c. However, all seven studies found the new rapid acting analogues achieved superior post-prandial glucose control, with smaller post-prandial glycaemic excursions. This occurred in all studies, both when regular insulin was administered 30-45mins pre-meal or when it was administered immediately pre-meal. It is difficult to be certain of the clinical significance of this improved post-prandial control.

The rapid action of the insulin analogues enables greater flexibility in dosing as they may be administered immediately pre-meal. Another potential advantage of the insulin analogue based regimens is a trend towards fewer hypoglycaemic episodes, though this was not a consistent finding in the trials.

Overall, the insulin analogues can be considered to provide greater flexibility and improved post-prandial glycaemic control. These small benefits may justify a
preference for these agents over human insulin equivalents; however their use may be restricted in many markets due to their higher cost.

**Comparison between different basal bolus regimens (n=2)**

Only two studies were identified which directly compared different basal bolus (QID) regimens (Sargin et al (2003) and Anderson et al (1997)).

The study by Sargin et al (2003) provided good data to support the rationale of a basal bolus regimen in type 2 diabetics who are inadequately controlled on twice daily insulin therapy. In this study, both basal bolus regimens achieved impressive reductions in HbA1c. The lispro based regimen reduced the mean HbA1c by 2.3%, whereas the regular insulin based regimen reduced it by a 1.5%. It is difficult to know how much of the superior glycaemic control observed with lispro can be attributed to lispro alone, as this regimen included twice daily NPH, whereas the regular insulin based regimen received once daily NPH; the rationale for the extra dose of NPH was that preprandial hyperglycaemia may occur with insulin lispro due to the short duration of action.

The second study by Anderson et al (1997) also compared lispro to regular human insulin in a basal bolus regimen. As in the studies of twice daily regimens, lispro improved post-prandial glycaemic control but this did not translate into a superior glycaemic control as assessed by HbA1c.

Overall, in these two studies, basal bolus regimens have been demonstrated to improve glycaemic control in type 2 diabetics patients who are inadequately controlled on their current insulin regimen. Insulin lispro affords the convenience of being able to dose immediately pre-meal and improves post-prandial glycaemic control. On this basis it should be preferred to regular human insulin as the prandial insulin of choice.

**Comparison of basal bolus regimen to insulin pump therapy (n=2)**

Only two studies comparing continuous insulin pump therapy to a basal bolus insulin regimen in type 2 diabetes were identified (Saudek et al (1996) and Raskin P et al (2003)).
HbA1c improved by a similar amount with either therapy. The study of the MiniMed implantable pump by Saudek et al (1996) revealed potential advantages of fewer hypoglycaemic episodes and less weight gain. However, the need for surgical implantation under general anaesthesia and potential problems with the pump leading to insulin under-delivery suggest that this treatment is probably not preferable to a basal bolus subcutaneous regimen.

Insulin pump therapy may be considered in patients who have inadequate control on a basal bolus regimen or those with problems with recurrent hypoglycaemia.

**Comparison of intensive vs less intensive insulin therapy (n=2)**

Two of the eligible studies undertook a randomised comparison between intensive insulin therapy vs ‘standard’ or ‘conventional’ insulin therapy (Abraira et al (1998) and Ohkubo et al (1995)).

The study by Abraira et al (1998) utilized a step wise escalation of therapy targeting aggressive control with compelling results. Bedtime basal insulin reduced HbA1c by 1.4%. When this failed, the addition of gliclazide achieved a further 0.5% reduction. Conversion to a twice daily insulin regimen only managed to maintain current HbA1c. And finally patients who progressed to require a basal bolus QID regimen achieved a further 0.6% reduction. Overall the intensive therapy group maintained an HbA1c approx 2% lower than the standard therapy group for over two years of follow-up. The downside of intensive therapy was significant increases in hypoglycaemic episodes, with each 0.5% fall in HbA1c leading to a doubling in the rate of reported hypos.

The second study by Ohkubo et al (1995) provided further compelling evidence as to the benefits of tight glycaemic control with insulin. A regimen consisting of multiple insulin injections achieved a 2% reduction in HbA1c (down to 7%). After six years of follow-up this tight control lead to significant reductions in the rate of development or progression of retinopathy or nephropathy.

Tight glycaemic control with insulin therapy is achievable and advantageous.
Insulin therapy in combination with metformin (n=13)

Comparisons of the addition of metformin to insulin vs insulin alone (n=8)

Most of these studies recruited patients who had inadequate glycaemic control on their current insulin containing regimen. As such, these patients have slightly more advanced diabetes than in trials evaluating the addition of sulfonylurea, where patients are more commonly insulin naive. Despite the relatively advanced diabetes, the addition of metformin leads to consistent benefits in glycaemic control, with additional advantages of less weight gain and lower daily insulin requirements.

Based on the pooled data from eight studies, the addition of metformin lead to a mean decrease in HbA1c of 1.15% (range 0 to -2.05%) over and above that which was achieved in the control group. The metformin group also gained a mean of 1.8kg less weight than the control group. The only down side to the addition of metformin was a significant increase in gastrointestinal complaints which lead to treatment discontinuation in several patients.

Overall, these studies support the addition of metformin in insulin requiring type 2 diabetics. The lack of an association with weight gain is an important therapeutic benefit of metformin, especially in type 2 diabetes where weight reduction is generally recommended. The avoidance of weight gain may partially explain the apparent benefits in the risk of macrovascular disease observed in obese patients in UKPDS who were assigned to metformin.

Miscellaneous comparisons of insulin + metformin and other regimens (n=5)
There were five other eligible studies evaluating the use of metformin in combination with insulin in various ways (Schwartz et al (2003), Yki-Jarvinen et al (1999), Janka et al (2005), Malone et al (2003) and Kilo et al (2003)).
The study by Schwartz et al (2003) compared triple oral therapy to a combination of Novolin70/30 bd + metformin in 188 patients with inadequate glycaemic control on two oral agents. Both options achieved similar improvements in HbA1c of just over 2% and weight gain was also similar. The authors argue that the insulin regimen should be preferred due its significantly lower cost. I suggest that either regimen could be considered and that triple oral therapy may be useful in patients who are eager to avoid insulin injections.

Yki-Jarvinen et al (1999) conducted a very useful head-to-head comparison of the addition of metformin or glyburide to bedtime NPH in 96 patients with secondary sulfonylurea failure. Use of metformin in combination with NPH was a clear winner based on the greatest reduction in HbA1c and the lack of weight gain. Interestingly, the group who received both metformin + glyburide + NPH did not derive additional benefit in terms of glycaemic control and lost the weight benefits seen with metformin alone. Four patients receiving metformin dropped out due to gastrointestinal side effects.

The study by Janka et al (2005) demonstrated insulin glargine + metformin + glimepiride to be superior to Mixtard 30/70 bd in 364 patients with secondary oral failure. The glargine based regimen achieved slightly superior glycaemic control and fewer hypoglycaemic episodes.

Malone et al (2003) suggested that the use of Mix25bd + metformin may be preferable to the combination of glibenclamide + metformin in patients with inadequate glycaemic control on a single oral agent. However the overall glycaemic control was similar between the groups, so I feel in most situations the addition of a second oral agent is preferable to the early initiation of insulin, as outlined in previous sections.

Kilo et al (2003) demonstrated comparable improvements in glycaemic control with three different metformin based regimens. The use of pre-dinner biphasic insulin was no more effective than bedtime NPH.
Summary of evidence supporting the use of insulin in combination with metformin

There is a significant base of evidence supporting the addition of metformin to patients with insulin requiring type 2 diabetes. Perhaps the most difficult question relates to the choice between continuing metformin vs a sulfonylurea (or both). Metformin achieves similar improvements in HbA1c to the addition of sulfonylureas. Metformin has additional benefits on other metabolic parameters, most notably weight gain, but perhaps also blood pressure and lipids. In view of these potential benefits, I recommend metformin be preferred in obese type 2 diabetics with secondary oral failure. In non-obese type 2 diabetics, it may be reasonable to recommend a sulfonylurea in view of their superior gastrointestinal tolerability. An alternate approach may be to have a trial of metformin first and switch to sulfonylurea only if the metformin is poorly tolerated.
Insulin use in combination with sulfonylurea (n=28)
The use of sulfonylureas in combination with insulin has been evaluated in the largest number of randomized clinical trials (n=28) of all the various oral agents. This combination is very commonly utilized in clinical practice and is particularly valuable in patients who prefer to avoid a regimen consisting of multiple daily injections of insulin.

Comparisons of the addition of a sulfonylurea to insulin vs addition of placebo/control to insulin (n=14)

The most commonly used sulfonylurea in these studies was glibenclamide (glyburide) (n=11). No studies conducted a head to head comparison between different sulfonylureas.

The design of these studies varied considerably making it difficult to pool or compare data from the different studies. Most of these studies only included 20-30 patients, with the largest study randomizing just 145 patients (Riddle M and Schneider J (1998)).

Many of the studies evaluated patients with secondary oral failure and thus even the control groups had significant falls in HbA1c upon the introduction of insulin. For this reason, it is most relevant to compare the difference in HbA1c and weight gain between groups, rather than the change from baseline alone. The benefits of sulfonylureas are also likely to be diminished somewhat in patients with secondary oral failure due to grossly impaired islet cell function. Some studies propose that fasting C-peptide levels may be used to help predict which patients will benefit from continuation/addition of sulfonylureas.
Overall in the fourteen eligible studies, the mean reduction in HbA1c attributable to the addition of sulfonylurea was -1.41% (range -2.9 to +0.3). The addition of sulfonylurea therapy (or continuing it when initiating insulin) lead to an increased risk of hypoglycaemia and to a mean weight gain of 0.94kg (range 0 to 2.5kg). The majority of the studies also demonstrated benefits with respect to reduction in the daily insulin requirements, though this is not consistently reported.

Based on these fourteen studies, there is adequate evidence to support the addition of or continuation of a sulfonylurea to insulin in type 2 diabetes. There is insufficient evidence to recommend the use of one sulfonylurea over the other. In many instances, patients will already be taking a sulfonylurea when they come to need insulin therapy, it would seem reasonable to continue their current sulfonylurea in this setting due to its established tolerability. Glibenclamide is the most widely studies agent and some clinicians may express a preference for this agent on this basis alone.

**Comparison of different insulin regimens in combination with sulfonylurea (n=10)**


Several of these studies make an important contribution to our current evidence base as they compare the regimens that clinicians and patients must chose between in the context of secondary oral failure. Several of these studies assume additional importance as they have randomised relatively large numbers of patients. (Stehouwer et al (2003) (n=261), Fritsche A et al (2003) (n=695), Bastyr E et al (2000) (n=131), Yki-Jarvinen H et al (1992) (n=149), Bastyr E et al (1999) (n=423), and Janka H et al (2005) (n=364))
Due to the number of different regimens compared, it is not possible to conduct a pooled analysis. Instead, I will give a brief overview of the key conclusions that may be drawn from each of these studies.

**Studies favouring multiple insulin injections:**

Stehouwer et al (2003) found that both Mixtard 30/70 bd and NPH bd achieved superior glycaemic control to bedtime NPH with glimepiride in their study of 261 obese patients with secondary oral failure. The tighter control with the twice-daily regimens came at the expense of a small increase in weight gain and increased rate of hypoglycaemia.

Bastyr et al (2000) undertook an interesting comparison between insulin lispro tds + glyburide, vs metformin + glyburide vs bedtime NPH + glyburide. Lispro had the greatest impact on overall metabolic control, but also the most weight gain and highest rate of hypoglycaemia. The metformin group enjoyed freedom from weight gain. NPH achieved the lowest FPG. This study highlights some of the different merits of each treatment and the challenges faced by clinicians and patients in selecting the best regimen for their circumstance.

Wolffenbuttel et al (1996) compared Mixtard bd to NPH + glibenclamide. There was a trend towards a greater reduction in HbA1c on Mixtard bd (-3.0% vs -2.5%). Continuing glibenclamide reduced daily insulin requirements. Weight gain and rate of hypoglycaemia was similar between groups. On balance, it would seem reasonable to offer either regimen to patients based on this trial.

Bastyr et al (1999) compared a QID lispro based regimen to tds lispro + sulfonylurea and NPH + sulfonylurea in 423 patients with secondary oral failure. The lispro regimens achieved marginally superior glycaemic control at the expense of more hypoglycaemia and multiple injections per day. The justification of lispro use as initial insulin therapy is fairly weak.

**Studies favouring single basal insulin dose:**

Lanststedt-Hallin et al (1995) found tds pre-prandial insulin + glibenclamide to be fairly comparable to bedtime NPH + glibenclamide overall, with both regimens
reducing HbAlc by around 2%. Postprandial control was superior on the tds regimen, while FPG was superior on NPH.

The study by Clauson et al (1996) found bedtime NPH + glimepiride to be preferable to a QID insulin regimen, as they achieved comparable glycaemic control (HbAlc - 2.5%), but the QID regimen lead to significantly more weight gain.

Fritsche et al (2003) conducted a large study in 695 patients with secondary oral failure. They demonstrated that insulin glargine + glimepiride was preferable to NPH + glimepiride, as it achieved marginally better glycaemic control with fewer nocturnal hypoglycaemia episodes.

Yki-Jarvinen et al (1992) conducted a very useful comparison of five different regimens commonly used in the context of secondary oral failure. They compared NPH + OHAs, Mixtard bd, a QID regimen and continued OHAs alone. Mean HbA1c improved by a similar amount on all the insulin containing regimens (mean -1.75%). On balance of glycaemic control, weight gain, risk of hypos and simplicity of regimen, this study would support a preference for bedtime NPH in combination with oral agents. Patients may require multiple injections as glycaemic control deteriorates.

The study by Janka et al (2005) compared insulin glargine + glimepiride + metformin to Mixtard bd in 364 patients with secondary oral failure. The glargine based regimen achieved superior glycaemic control with less hypoglycaemia and should be preferred on this basis.

Chow et al (1995) also provide date supporting use of oral agents in combination with insulin. Bedtime NPH + OHAs achieved comparable glycaemic control to twice daily insulin alone, with significantly less weight gain.

**Comparisons of insulin + sulfonylurea to orals alone (n=2)**

In addition to the studies which compared oral agents to various insulin regimens previously discussed, there were also 2 studies identified which compared the combination of insulin + sulfonylurea to the combination of metformin + sulfonylurea.
The study by Niazi and Muzaffer (1998) adds very little to the evidence base due to the fact that 50% of patients randomized to insulin discontinued it. The authors report that Pakistanis have beliefs against the use of daily injections, which limit its use in that cultural setting.

The study by Klein (1991) also has some methodological concerns, as 30% of randomized patients were excluded from the final analysis. Nonetheless, impressive HbA1c reductions of around 4% were achieved on both regimens.

These two studies add very little to the balance of evidence but are consistent with my previously recommended preference for combination oral therapy prior to insulin initiation in most settings.

Comparisons of insulin + sulfonylurea to the addition of an alternate oral agent (n=2)

Yki-Jarvinen (1999) undertook a very useful comparison between four simple basal insulin based regimens commonly used in clinical practice when oral agents have failed to achieve adequate glycaemic control. Bedtime NPH + metformin, vs bedtime NPH + glyburide, vs bedtime NPH + metformin + glyburide, vs twice daily NPH. After 12 months follow-up all four regimens achieved significant improvements in HbA1c of around 2%. The combination of metformin with bedtime NPH emerged as a fairly convincing winner, due to a combination of the greatest improvement in HbA1c (-2.5%), the least weight gain (approx 3kg less than other regimens) and the lowest rate of hypoglycaemia. This trial provides fairly compelling evidence to support a preference for continuation of metformin, over sulfonylureas when basal insulin is initiated in type 2 diabetes. The major limiting factor for metformin use in this setting will be gastrointestinal tolerability.

The small study by Guvener and Gedik (1999) compared the addition of sulfonylurea to the addition of acarbose. Both regimens achieved similar improvements in HbA1c of just over 1%. The acarbose group gained less weight and required less insulin. The authors conclude that acarbose seems preferable to gliclazide for use in combination with insulin. However, I don't feel this study provides adequate evidence to justify
such a preference, as the balance of evidence suggests that acarbose is less effective in improving glycaemic control and has significant gastrointestinal side effects that limit its use (see subsequent chapter on the use of acarbose with insulin)

Summary of evidence supporting the use of insulin in combination with sulfonylurea
There is a large base of evidence from over 3,000 patients in randomised clinical trials supporting both the continuation of and the addition of sulfonylureas to patients with type 2 diabetes who require insulin. Most of these trials have been conducted in patients with secondary oral failure – this stems from the established preference to utilize combinations of oral agents prior to initiating insulin (which is supported by UKPDS).

The addition or continuation of sulfonylurea will improve glycaemic control, with additional reductions of HbA1c of over 1% generally being observed where it is combined with a simple regimen of once daily basal insulin. In this context it achieves fairly comparable glycaemic control to more intensive regimens consisting of multiple daily injections of insulin alone (Yki-Jarvinen H et al (1992)). The advantages of commencing with a regimen of once daily long-acting insulin + sulfonylurea compared to a multiple daily insulin regimen include less weight gain, lower daily insulin requirements, fewer hypoglycaemia episodes and greater simplicity for the patient.

With the passage of time many patients will progress to require a more intensive insulin regimen at which time continuation of the oral agents is of limited value.
Insulin use in combination with glitazones (n=5)


Four of the five studies randomised diabetic patients with inadequate glycaemic control on insulin alone, to receive placebo, or either a high or low-dose glitazone (Buse J. et al (1998), Schwartz S et al (1998), Raskin et al (2001), Rosenstock J et al (2002). In all four studies there was clear evidence of a dose response with respect to glycaemic control and adverse effects. One study by Strowig S et al (2002) compared the addition of placebo, troglitazone or metformin to insulin, in patients with inadequate glycaemic control on insulin alone.

Based on the pooled data, the addition of high dose glitazone therapy (troglitazone 600mg, rosiglitazone 8mg or pioglitazone 30mg) lead to a mean reduction in HbA1c of 1.1% (range 0 to -2.1%). Daily insulin requirements were also consistently reduced in all studies. Mean weight gain across the studies was 3.4kg (range 0 to +5.3kg).

The addition of low dose glitazone therapy (troglitazone 200mg, rosiglitazone 4mg, pioglitazone 15mg) produced consistent, smaller improvements in glycaemic control than the higher doses. The mean reduction in HbA1c was 0.6% (range 0 to -0.99%). Mean weight gain on the lower dose was 2.05kg (range 0 to +4kg). Daily insulin requirements were also consistently reduced.

The addition of glitazones also increased the risk of hypoglycaemia and lead to reports of oedema in approx 15% of patients. Fluid retention is likely to be a key component of the weight gain observed on glitazones and has lead to these agents being contraindicated in patients with cardiac failure.

The study by Strowig S et al (2002) demonstrated slightly superior improvements in HbA1c with troglitazone compared to metformin. However, this came at the expense of more weight gain and increased risk of hypoglycaemia.
Overall, the addition of glitazones leads to significant improvements in glycaemic control and enables insulin doses to be reduced. It does so at a cost of extra hypoglycaemic episodes, fluid retention and weight gain.

The addition of a glitazone to insulin therapy should therefore be considered as an alternative to the combination of metformin with insulin, or sulfonylurea. However, currently both sulfonylureas and metformin have a more extensive evidence base and are appreciably cheaper than glitazones, making them the preferred option for most patients.
Insulin use in combination with acarbose (n=6)


Four of these studies directly compared the addition of acarbose to the addition of placebo (Coniff R et al (1995), Hwu et al (2003), Kelley D et al (1998), Chiasson JL et al (1994)). These studies demonstrated that the addition of acarbose leads to a consistent small reduction in HbA1c (mean -0.45% range 0 to -0.7%). The improved HbA1c was largely driven by improved post-prandial glycaemic control. The addition of acarbose also leads to small decreases in daily insulin requirements. Adverse gastrointestinal effects, particularly flatulence, abdominal cramps and diarrhea were common with acarbose and significantly limit the role of acarbose.

One study by Guvener and Gedik (1999) compared the combination of insulin + acarbose, with the combination of insulin + gliclazide. Both combinations achieved similar improvements in HbA1c of just over 1%, but acarbose had tolerability problems with flatulence and bloating.

Standle et al (1999) evaluated the addition of acarbose or placebo to a regimen of insulin + glibenclamide. Both arms achieved a significant 2.4% reduction in HbA1c, which was largely attributable to the modified insulin regimen. The only important benefit of the addition of acarbose was a reduction in insulin requirements of 7u/day. This occurred at the expense of a significant increase in gastrointestinal side effects and does not warrant use of acarbose in this setting.

Overall, the combination of other oral agents with insulin should be preferred to the combination of acarbose and insulin, due to superior tolerability and greater improvements in glycaemic control. Acarbose may have a role in patients where post-prandial hyperglycaemia is problematic or as a third line oral hypoglycaemic agent.
General comments
The target HbA1c for patients with type 2 diabetes has progressively fallen over the past few decades as the benefits of tight glycaemic control have been convincingly demonstrated. The lower targets currently being recommended in clinical practice are apparent both in clinical trial designs and in the level of glycaemic control apparent in clinical trial patients at baseline. And yet even in a clinical trial setting many patients fail to achieve the targets. Nonetheless, as glycaemic control improves and the therapeutic armamentarium grows larger, it is becoming increasingly difficult for new agents to demonstrate that they provide an important therapeutic advance.

Reporting of hypoglycaemia has become more important as target HbA1c has fallen. In general, tighter glycaemic control increases the risk of hypoglycaemia. Many studies included in my analysis, reported hypoglycaemia rates inadequately or not at all. The quality and consistency of reporting has improved in recent years, making comparison between different trial results somewhat easier. There is clearly a need for patients and their relatives to be educated as to the symptoms of hypoglycaemia and recognize the need to intervene early.

There is currently no consensus among physicians and experts about the proper schedule for the administration of insulin in patients with type 2 diabetes. The large number of regimens available serves to increase uncertainty and may be somewhat overwhelming for clinicians. In the absence of specific clear recommendations, it is useful to consider the following general guidance as to the use of insulin in type 2 diabetes:

- Develop expertise in a limited number of regimens (to allow for patient preferences, lifestyle, etc.) and use them consistently.
- Insulin resistance creates the potential need for large doses of insulin. In the usual patient with type 2 diabetes, the dose is in the range of 0.6 to 1.0 units/kg per 24 hours.

Insulin therapy in Type 2 diabetes
Conclusions and Recommendations
• Once a regimen has been chosen, increase doses incrementally until glycaemic targets are achieved. It is preferable to avoid frequent changes to the insulin regimen, as this will tend to delay the achievement of goals and may confuse, frustrate and demoralize the patient.

• Keep it simple. In many patients with type 2 diabetes, a single dose of insulin per day is sufficient. The need for multiple doses of insulin becomes apparent if control remains suboptimal on high doses of basal insulin or if control is only acceptable at certain times of the day.

Evidence-based treatment recommendations

In September 2002, the National Institute for Clinical Excellence concluded (McIntosh A et al 2001):

"Insulin therapy should be offered to people with diabetes with inadequate blood glucose control on optimised oral glucose-lowering drugs."

In addition they recommended that:

"Local experience, patient preference and relative costs should inform the choice of insulin type and regimen as there is little research evidence in this area"

Based on my review of the evidence, both of these statements remain partially true. However, I believe there is now adequate evidence to support the benefits of specific agents and of a stepwise approach to the introduction of insulin as outlined below. Like many therapeutic areas, the ‘best’ treatment will depend on an assessment of a number on patient factors and perhaps most importantly on patient preference. In many ways we are fortunate to be in a position of having multiple treatment options, which enables patients to choose which suits their needs the best.
Proposed insulin treatment algorithm

Initial diagnosis: Diet and Exercise (see note 1)

HbA1c>7.0%

Oral hypoglycaemic therapy (see note 2)

HbA1c>7.0%

Metformin (if obese)

Sulfonylurea (if non-obese)

HbA1c>7.0%

HbA1c>7.0%

Metformin +/- Sulfonylurea (see note 3)

HbA1c>7.0%

Add Glitazone (see note 4)

Add basal insulin once daily (see note 5)

Add prandial insulin QID regime (see note 6)

Change to mixture of basal + prandial insulin twice daily (see note 7)
Treatment algorithm explanatory notes

Note 1:
Patients with type 2 diabetes should be treated in a step-wise manner. Initially attempts should be made to normalise glycaemia using diet and exercise, with weight loss if overweight. Considerable improvements in glycaemia can be achieved through a combination of diet and exercise.

Note 2:
When patients fail to achieve adequate glycaemic control on dietary therapy alone, initiation of an oral hypoglycaemic agent is appropriate. The most compelling data supporting first line use of oral agents comes from UKPDS where patients assigned to intensive insulin from the outset experienced comparable glycaemic control to those taking oral agents, but suffered greater weight gain and more frequent hypoglycaemia. Consideration of which oral agent to use first is beyond the scope of this dissertation, but most clinicians recommend metformin in obese patients, due to a lack of weight gain and potential cardiovascular benefits. Non-obese patients will often commence a sulfonylurea due to superior tolerability and comparable glycaemic control.

Note 3:
If glycaemic control deteriorates further on monotherapy, it is appropriate to add a second agent (sulfonylurea or metformin). Some clinicians argue that in order to reach the latest aggressive HbA1c targets of 6.5% or 7% it may be appropriate to add insulin earlier, rather than a second oral agent. This would seem a reasonable approach in patients with very poor glycaemic control (HbA1c>9.0%), as usually the addition of a second oral agent will only reduce HbA1c by approximately 1-2%. However, most patients express a preference to avoid injections if possible and so I would advocate a trial of additional oral therapy in combination with reiterating the importance of adhering to diet and exercise recommendations. Some patients may be more compliant with lifestyle recommendations, if they are motivated to avoid insulin injections. Patients who do not tolerate metformin due to gastrointestinal side effects may also be considered as candidates for a glitazone in combination with sulfonylurea, prior to initiating insulin.
Patients with secondary oral failure on maximal doses of a combination of metformin +/- sulfonylurea have several different options. The addition of a third oral agent is a reasonable choice, particularly in those patients who express a preference to avoid insulin injections. The glitazones have been shown to improve glycaemic control in this setting, though the total cost of triple oral therapy may be higher than that of initiating insulin therapy.

Acarbose may be considered an option by some patients and clinicians, but it has only a very limited role in therapy due to its poor gastrointestinal tolerability and relatively small impact on glycaemic control. It has a role to play in patients whose major problem is post-prandial glycaemic control, or in patients with contraindications to the alternative oral agents.

Patients who chose to add a glitazone to their dual oral therapy will ultimately require addition of insulin as their glycaemic control deteriorates. Glitazones are not licensed for use in combination with insulins in all markets, but they do have evidence to support their role in this capacity. Similar to sulfonylureas and metformin, the use of a glitazone in combination with insulin has been shown to further improve glycaemic control and to reduce insulin requirements. They do so at a cost of increased weight gain (largely due to fluid retention) and remain relatively expensive agents. I feel the currently available data favours the use of metformin in combination with insulin, over glitazones in combination with insulin, especially in view of cost considerations.

Note 5:
Several studies have shown that the addition of a single dose of basal insulin may lead to a substantial improvement in FPG and HbA1c. I believe this is the option of choice for patients with secondary oral failure on metformin/sulfonylurea who are willing to have injections. Most patients with type 2 diabetes will ultimately require insulin due to the progressive nature of the disease – use of a once daily dose of insulin is a safe and effective means of improving glycaemic control without being overly daunting to the patient.
I recommend continuation of the oral agents at least initially, in part to ensure that glycaemic control doesn’t deteriorate upon initiation of insulin which may be very disillusioning for the patient. Both metformin and sulfonylurea have been shown to improve glycaemic control when used in combination with insulin (over insulin alone). Continued oral agents will also reduce total insulin requirements and lead to superior post-prandial glycaemic control – which may be inadequate on once daily basal insulin alone.

**What are the benefits of continuation of a sulfonylurea?**

There is a large base of evidence supporting both the continuation and the addition of sulfonylureas to patients with type 2 diabetes who require insulin. They are generally well tolerated, but hypoglycaemic can be problematic. There is insufficient evidence to recommend the use of one sulfonylurea over the other. In patients already taking a sulfonylurea when they come to need insulin therapy, it is sensible to continue their current sulfonylurea in this setting due to its established tolerability. Glibenclamide is the most widely studies agent, however some clinicians prefer to use gliclazide due to its shorter duration of action.

Addition or continuation of sulfonylurea will improve glycaemic control, with additional reductions of HbA1c of over 1% generally being observed where it is combined with a simple regimen of once daily basal insulin. In this context it achieves fairly comparable glycaemic control to more intensive regimens consisting of multiple daily injections of insulin alone. The advantages of commencing with a regimen of once daily long-acting insulin + sulfonylurea compared to a multiple daily insulin regimen include less weight gain, lower daily insulin requirements, fewer hypoglycaemia episodes and greater simplicity for the patient.

Some studies have attempted to classify patients into responders and non-responders – it may be useful to assess fasting C-peptide levels in insulin requiring diabetics, to help assess if they are likely to benefit from the addition/continuation of a sulfonylurea. Patients without evidence of residual endogenous insulin secretion are likely to derive less benefit.
What are the benefits of continuation of metformin?
Metformin achieves similar improvements in HbA1c to the addition of a sulfonylurea. Metformin has additional benefits on other metabolic parameters, most notably weight gain, but perhaps also blood pressure and lipids. The lack of an association with weight gain is an important therapeutic benefit of metformin, especially in type 2 diabetes where weight reduction is generally recommended. Avoidance of weight gain may partially explain the apparent benefits in the risk of macrovascular disease observed in obese patients in UKPDS who were assigned to metformin.

In view of these potential benefits I recommend metformin be preferred to sulfonylureas in obese type 2 diabetics with secondary oral failure. In non-obese type 2 diabetics, it may be reasonable to recommend a sulfonylurea in view of their superior gastrointestinal tolerability. An alternate approach may be to have a trial of metformin first and switch to sulfonylurea only if the metformin is poorly tolerated.

Why should insulin glargine be preferred to NPH insulin?
Insulin glargine is preferable to NPH as its peakless profile more closely mimics physiological basal insulin secretion. The absence of a peak reduces the risk of nocturnal hypoglycaemia, which can be problematic with bedtime NPH. Insulin glargine may also provide superior post-dinner glycaemic control than NPH due to its longer duration of action.

However, insulin glargine is yet to convincingly demonstrate superior glycaemic control as assessed by HbA1c, compared to NPH. It is possible that in real-world clinical practice reduced fear of nocturnal hypoglycaemia with glargine may improve adherence to insulin therapy and thus improve glycaemic control (de Sonnaville J et al. 1998).

Insulin glargine is significantly more expensive than NPH and is not reimbursed in some markets (including Australia as at September 2005). As a result its use may be limited to those patients who derive the greatest benefit in particular those who have had problems with recurrent nocturnal hypos on NPH.
Due to the progressive nature of type 2 diabetes, many patients will ultimately require multiple daily injections of insulin. Oral agents become less efficacious in advanced β-cell dysfunction. As β-cell secretory function declines, exogenous insulin requirements will increase and glycaemic control on once daily insulin (+/- OHAs) may become inadequate. In this setting, there is good evidence supporting the role of multiple daily injections of insulin.

QID regimen vs mixed insulin twice daily?
A QID regimen consisting of bedtime long-acting insulin (NPH or glargine) and prandial short-acting insulin comes closest to mimicking normal insulin secretion, but there is insufficient data to demonstrate that it is superior to a twice daily regimen consisting of a mixture of NPH and short-acting insulin. The choice of a QID regimen vs a twice daily regimen must therefore be guided by physician and patient preference.

Rapid acting insulin analogues vs regular human insulin?
There is some evidence that the newer rapid acting insulin analogues are superior to regular human insulin. Their faster onset of action enables greater flexibility in dosing time, as they can be administered immediately pre-prandially; this is particularly useful to patients with unpredictable meal times or erratic eating habits. Another key benefit of the rapid-acting analogues is their superior post-prandial glycaemic control compared to regular human insulin. However, this has not been demonstrated to achieve superior glycaemic control as assessed by HbA1c. A further limitation of the newer agents is their higher cost. Overall, I feel that there is sufficient evidence to recommend the use of the rapid-acting analogues over regular human insulin in systems where they are reimbursed.

Any benefit of continuation of orals?
Once patients have progressed to a QID insulin regimen, there is little benefit to be gained from continuation of sulfonylureas due to beta-cell exhaustion. I recommend continuation of metformin if tolerated due to benefits as previously outlined. Glitazones may also have a role in helping to preserve beta-cell function.
Patients who wish to avoid a QID insulin regimen should be offered a twice daily regimen. Twice daily administration of NPH and short acting insulin has been shown to significantly improve glycaemic control in patients with inadequate control on once daily insulin (+/- OHAs).

The intermediate and short-acting insulins may be administered separately or as one of the commercially available ‘pre-mixed’ insulin preparations (eg. Mixtard 30/70). Separate administration has the advantage of enabling more complex dose adjustments and more reliable retention of the different pharmacokinetic profiles of the two agents. Advantages of using pre-mixed insulin include simplification for the patient and a decrease in the number of injections required. The choice between the two should be dictated by physician and patient preference.

**Any benefit of continuation of orals?**
Once patients have progressed to a twice daily insulin regimen, the issues with respect to use of orals are similar to those outlined above for patients on QID insulin. Metformin should be continued where tolerated and consideration may be given to the use of glitazones (in countries where it is licensed for use in combination with insulin).

**What is the role of newer premixed formulations of insulin analogues?**
Pre-mixed formulations of the newer rapid-acting insulins are now also available (eg. Mix25, BIAsp25) with similar advantages to those outlined above in note 6. Their use should be guided by physician and patient preference, as well as subsidised availability.

**Note 7:**
Patients who wish to avoid a QID insulin regimen should be offered a twice daily regimen. Twice daily administration of NPH and short acting insulin has been shown to significantly improve glycaemic control in patients with inadequate control on once daily insulin (+/- OHAs).
Conclusions
The benefits of tight glycaemic control in type 2 diabetes are now clearly established. Patients should be educated as to these benefits and understand the goals of treatment. The progressive nature of type 2 diabetes means that most patients will ultimately require multiple therapies to achieve acceptable glycaemic control. Insulin has a vital role to play in the management of type 2 diabetes and patients should be counselled as to the expectation of requiring insulin at some stage during the course of their management.

The step-wise treatment algorithm I have proposed takes account of clinical data from 88 randomised controlled trials undertaken in this arena. Despite this extensive evidence base, some treatment decisions must be made in the face of an incomplete data. In this setting, it is important to discuss the potential pros and cons of different options with the patient, so that they can make an informed choice as to which suits their individual needs the best.

REFERENCES
## Appendix 1 – MEDLINE Search String (executed December 20th 2003)

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<td>limit 32 to english language</td>
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<tr>
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Appendix 3: MEDLINE Eligible Studies after title and abstract review
(n=58)

The MEDLINE search yielded a total of 177 studies. After reviewing all titles and abstracts 58 were considered eligible for further evaluation.

1. Authors - HOE 901/2004 Study Investigators Group.
Title - Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients.

Title - Combination of insulin and metformin in the treatment of type 2 diabetes.

3. Authors - Herz M. Arora V. Campagne BN. Scholtz HE. Potgieter MA. Mollentze W.
Title - Humalog Mix25 improves 24-hour plasma glucose profiles compared with the human insulin mixture 30/70 in patients with type 2 diabetes mellitus.

4. Authors - Strowig SM. Aviles-Santa ML. Raskin P.
Title - Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes.

5. Authors - Herz M. Profozic V. Arora V. Smircic-Duvnjak L. Kovacevic I. Boras J. Campagne BN. Metelko Z.
Title - Effects of a fixed mixture of 25% insulin lispro and 75% NPL on plasma glucose during and after moderate physical exercise in patients with type 2 diabetes.
6. Authors - UK Prospective Diabetes Study (UKPDS) Group.
Title - Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group.

7. Authors - Turner RC. Cull CA. Frighi V. Holman RR.
Title - Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group.

# UKPDS 33 and UKPDS 49 utilise the same study participants and will be considered as one study for the purpose of any meta-analysis conducted. I have included them both as they provide different relevant data.

8. Authors - Schwartz S. Raskin P. Fonseca V. Graveline JF.
Institution - Diabetes and Glandular Diseases Clinic, San Antonio, Tex., USA.
Title - Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. Troglitazone and Exogenous Insulin Study Group.

Title - A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes.

10. Authors - Rosenstock J. Schwartz SL. Clark CM Jr. Park GD. Donley DW. Edwards MB.
Title - Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin.

11. Authors - Yki-Jarvinen H. Dressler A. Ziemen M. HOE 901/300s Study Group.
Title - Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group.
Source - Diabetes Care. 23(8):1130-6, 2000 Aug.

12. Authors - Boehm BO. Home PD. Behrend C. Kamp NM. Lindholm A.
Institution - Universitatsklinikum Ulm, Ulm, Germany. bernhardm@medizin.uni-ulm.de
Title - Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients.

13. Authors - Zargar AH. Masoodi SR. Laway BA. Wani Al. Bashir MI.
Title - Response of regimens of insulin therapy in type 2 diabetes mellitus subjects with secondary failure.

Title - Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy.

15. Authors - Herz M. Sun B. Milicevic Z. Erickson P. Fovenyi J. Grzywa M. Pelikanova T.
Title - Comparative efficacy of preprandial or postprandial Humalog Mix75/25 versus glyburide in patients 60 to 80 years of age with type 2 diabetes mellitus.

Title - Long-term glycaemic improvement after addition of metformin to insulin in insulin-treated obese type 2 diabetes patients.
Source - Diabetes, Obesity & Metabolism. 3(6):428-34, 2001 Dec.

Title - A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents.

Title - Glycemic control with Humalog Mix25 in type 2 diabetes inadequately controlled with glyburide.

19. Authors - Ponssen HH. Elte JW. Lehert P. Schouten JP. Bets D.
Title - Combined metformin and insulin therapy for patients with type 2 diabetes mellitus.

20. Authors - Guvener N. Gedik O.
Title - Effects of combination of insulin and acarbose compared with insulin and gliclazide in type 2 diabetic patients.
21. Authors - Aviles-Santa L. Sinding J. Raskin P.
Title - Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial.

22. (Citation 69).
Medline Identifier - 21121581
Authors - Standl E. Baumgartl HJ. Fuchtenbusch M. Stemplinger J.
Institution - Institute of Diabetes Research and Department of Endocrinology, Academic Hospital Schwabing, Koelner Plate 1, Munich, Germany.
Title - Effect of acarbose on additional insulin therapy in type 2 diabetic patients with late failure of sulphonylurea therapy.

23. Authors - Abraira C. Henderson WG. Colwell JA. Nuttall FQ. Comstock JP. Emanuele NV. Levin SR. Sawin CT. Silbert CK.
Title - Response to intensive therapy steps and to glipizide dose in combination with insulin in type 2 diabetes. VA feasibility study on glycemic control and complications (VA CSDM).

24. Authors - Niazi R. Muzaffar Z.
Title - Comparison of bedtime NPH insulin or metformin combined with glibenclamide in secondary sulphonylurea failure in obese type II (NIDDM) patients.

25. Authors - Tovi J. Ingemansson SO. Engfeldt P.
Title - Insulin treatment of elderly type 2 diabetic patients: effects on retinopathy.
26. Authors - Relimpio F. Pumar A. Losada F. Mangas MA. Acosta D. Astorga R.
Title - Adding metformin versus insulin dose increase in insulin-treated but poorly controlled Type 2 diabetes mellitus: an open-label randomized trial.

27. Authors - Buse JB. Gumbiner B. Mathias NP. Nelson DM. Faja BW. Whitcomb RW.
Title - Troglitazone use in insulin-treated type 2 diabetic patients. The Troglitazone Insulin Study Group.

28. Authors - Penfornis A. Millot L.
Title - Initiating insulin treatment in insulin-requiring type 2 diabetic patients: comparative efficiency and cost of outpatient and inpatient management. INNOV Study Group.

29. Authors - Birkeland KI. Rishaug U. Hanssen KF. Vaaler S.
Title - NIDDM: a rapid progressive disease. Results from a long-term, randomised, comparative study of insulin or sulphonylurea treatment.

30. Authors - Fanghanel G. Sanchez-Reyes L. Trujillo C. Sotres D. Espinosa-Campos J.
Title - Metformin's effects on glucose and lipid metabolism in patients with secondary failure to sulfonylureas.

31. Authors - Ravnik-Oblak M. Mrevlje F.
Title - Insulin versus a combination of insulin and sulfonylurea in the treatment of NIDDM patients with secondary oral failure.
32. Authors - Calle-Pascual AL. Garcia-Honduvilla J. Martin-Alvarez PJ. Vara E. Calle JR. Munguira ME. Maranes JP.
Title - Comparison between acarbose, metformin, and insulin treatment in type 2 diabetic patients with secondary failure to sulfonylurea treatment.

33. Authors - Ohkubo Y. Kishikawa H. Araki E. Miyata T. Isami S. Motoyoshi S. Kojima Y. Furuyoshi N. Shichiri M.
Title - Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study.
Source - Diabetes Research & Clinical Practice. 28(2):103-17, 1995 May.

34. Authors - Landstedt-Hallin L. Adamson U. Arner P. Bolinder J. Lins PE.
Title - Comparison of bedtime NPH or prandial regular insulin combined with glibenclamide in secondary sulfonylurea failure.

35. Authors - Coniff RF. Shapiro JA. Seaton TB. Hoogwerf BJ. Hunt JA.
Title - A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes.

36. Authors - Chow CC. Tsang LW. Sorensen JP. Cockram CS.
Title - Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients.

37. Authors - Riddle M. Hart J. Bingham P. Garrison C. McDaniel P.
Title - Combined therapy for obese type 2 diabetes: suppertime mixed insulin with
daytime sulfonylurea.

38. Authors - Karlander SG. Gutniak MK. Efendic S.
Title - Effects of combination therapy with glyburide and insulin on serum lipid levels in
NIDDM patients with secondary sulfonylurea failure.

39. Authors - Klein W.
Title - Sulfonylurea-metformin-combination versus sulfonylurea-insulin-combination in
secondary failures of sulfonylurea monotherapy. Results of a prospective randomized
study in 50 patients.

40. Authors - Groop L. Widen E.
Title - Treatment strategies for secondary sulfonylurea failure. Should we start insulin or
add metformin? Is there a place for intermittent insulin therapy?.

41. Authors - Paterson KR. Wilson M. Kesson CM. Buchan M. Roberts M. Reith SB.
Davidson E.
Title - Comparison of basal and prandial insulin therapy in patients with secondary
failure of sulphonylurea therapy.

42. Authors - Sotaniemi EA. Vierimaa E. Huupponen R. Karvonen I. Vuoti MJ. Rytomaa
K.
Title - Insulin and sulphonylurea in the therapy of type 2 diabetes.
43. Authors - Simpson HC. Sturley R. Stirling CA. Reckless JP.  
Title - Combination of insulin with glipizide increases peripheral glucose disposal in secondary failure type 2 diabetic patients.  

44. Authors - Groop L. Widen E. Franssila-Kallunki A. Ekstrand A. Saloranta C. Schalin C. Eriksson J.  
Title - Different effects of insulin and oral antidiabetic agents on glucose and energy metabolism in type 2 (non-insulin-dependent) diabetes mellitus.  

45. Authors - Wolffsenbuttel BH. Weber RF. van Koetsveld PM. Weeks L. Verschoor L.  
Title - A randomized crossover study of sulphonylurea and insulin treatment in patients with type 2 diabetes poorly controlled on dietary therapy.  

46. Authors - Lewitt MS. Yu VK. Rennie GC. Carter JN. Marel GM. Yue DK. Hooper MJ.  
Title - Effects of combined insulin-sulfonylurea therapy in type II patients.[comment].  

47. Authors - Casner PR.  
Title - Insulin-glyburide combination therapy for non-insulin-dependent diabetes mellitus: a long-term double-blind, placebo-controlled trial.  

48. Authors - Lins PE. Lundblad S. Persson-Trotzig E. Adamson U.  
Title - Glibenclamide improves the response to insulin treatment in non-insulin-dependent diabetics with second failure to sulfonylurea therapy.  
49. Authors - Reich A. Abraira C. Lawrence AM.
Title - Combined glyburide and insulin therapy in type II diabetes.

50. Authors - Gutniak M. Karlander SG. Efendic S.
Title - Glyburide decreases insulin requirement, increases beta-cell response to mixed meal, and does not affect insulin sensitivity: effects of short- and long-term combined treatment in secondary failure to sulfonylurea.

51. Authors - Holman RR. Steemson J. Turner RC.
Title - Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement.

52. Authors - Samanta A. Burden AC. Kinghorn HA.
Title - A comparative study of sulphonylurea and insulin therapy in non insulin dependent diabetics who had failed on diet therapy alone.

53. Authors - Quatraro A. Consoli G. Ceriello A. Giugliano D.
Title - Combined insulin and sulfonylurea therapy in non-insulin-dependent diabetics with secondary failure to oral drugs: a one year follow-up.

54. Authors - Mauerhoff T. Ketelslegers JM. Lambert AE.
Title - Effect of glibenclamide in insulin-treated diabetic patients with a residual insulin secretion.

55. Authors - Falko JM. Osei K.
Title - Combination insulin/glyburide therapy in type II diabetes mellitus. Effects on lipoprotein metabolism and glucoregulation.

56. Authors - Groop L. Harno K. Nikkila EA. Pelkonen R. Tolppanen EM.
Title - Transient effect of the combination of insulin and sulfonylurea (glibenclamide) on glycemic control in non-insulin dependent diabetics poorly controlled with insulin alone.

57. Authors - Groop L. Harno K. Tolppanen EM.
Title - The combination of insulin and sulphonylurea in the treatment of secondary drug failure in patients with type II diabetes.
Appendix 4: MEDLINE Excluded Studies after title and abstract review  
(n=119)

Out of 177 studies yielded by the MEDLINE search, 119 were considered ineligible for inclusion in the systematic review. All the excluded studies have been grouped below according to reason for exclusion.

1. Not a randomised controlled trial (n=24)

1. Authors - DeWitt DE. Hirsch IB.  
Title - Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review.  

2. Authors - Chan JL. Abrahamson MJ.  
Title - Pharmacological management of type 2 diabetes mellitus: rationale for rational use of insulin. [Review] [78 refs]  

3. Authors - Davis TM. Clifford RM. Davis WA. Fremantle Diabetes Study.  
Title - Effect of insulin therapy on quality of life in Type 2 diabetes mellitus: The Fremantle Diabetes Study.  

4. Authors - Chapman TM. Noble S. Goa KL.  
Title - Insulin aspart: a review of its use in the management of type 1 and 2 diabetes mellitus. [Review] [100 refs]  

5. Authors - Chapman TM. Noble S. Goa KL.  
Title - Insulin aspart: a review of its use in the management of type 1 and 2 diabetes
mellitus. [Review] [100 refs]

6. Authors - Campbell RK. White JR Jr.
Title - Insulin therapy in type 2 diabetes. [Review] [46 refs]

7. Authors - Vaaler S.
Title - Optimal glycemic control in type 2 diabetic patients. Does including insulin treatment mean a better outcome?. [Review] [23 refs]

8. Authors - Goddijn PP. Bilo HJ. Feskens EJ. Groeniert KH. van der Zee KI. Meyboom-de Jong B.
Title - Longitudinal study on glycaemic control and quality of life in patients with Type 2 diabetes mellitus referred for intensified control.

9. Authors - Berger M. Jorgens V. Muhlhauser I.
Title - Rationale for the use of insulin therapy alone as the pharmacological treatment of type 2 diabetes. [Review] [40 refs]

10. Authors - Nauck MA. Sauerwald A. Ritzel R. Holst JJ. Schmiegel W.
Title - Influence of glucagon-like peptide 1 on fasting glycemia in type 2 diabetic patients treated with insulin after sulfonylurea secondary failure.

11. Authors - Bertin E. Rich N. Schneider N. Larbre H. Marcus C. Durlach V. Leutenegger M.
Title - Insulin and body fat distribution have no direct effect on plasma leptin levels in obese Caucasian women with and without type 2 diabetes mellitus.

12. Authors - Davey P. Grainger D. MacMillan J. Rajan N. Aristides M. Gliksman M.
Title - Clinical outcomes with insulin lispro compared with human regular insulin: a meta-analysis.

13. Authors - Johnson JL. Wolf SL. Kabadi UM.
Title - Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials.

14. Authors - Genuth S.
Title - Exogenous insulin administration and cardiovascular risk in non-insulin-dependent and insulin-dependent diabetes mellitus.

15. Authors - Kayashima T. Yamaguchi K. Konno Y. Nanimatsu H. Aragaki S. Shichiri M.
Title - Effects of early introduction of intensive insulin therapy on the clinical course in non-obese NIDDM patients.

16. Authors - Lindstrom T. Eriksson P. Olsson AG. Arnvist HJ.
Title - Long-term improvement of glycemic control by insulin treatment in NIDDM patients with secondary failure.

17. Authors - Pugh JA. Wagner ML. Sawyer J. Ramirez G. Tuley M. Friedberg SJ.
Title - Is combination sulfonylurea and insulin therapy useful in NIDDM patients? A metaanalysis.

18. Authors - Lindstrom TH. Arnqvist HJ. von Schenck HH.
Title - Effect of conventional and intensified insulin therapy on free-insulin profiles and glycemic control in NIDDM.

19. Authors - Peters AL. Davidson MB.
Title - Insulin plus a sulfonylurea agent for treating type 2 diabetes.

20. Authors - Liu D. Wettergren M. Lins PE. Adamson U.
Title - Combined insulin-glibenclamide therapy of NIDDM patients in primary health care. A follow-up study of its compliance and efficacy and a review of the literature.

21. Authors - Mohan V. Snehalatha C. Ramachandran A. Viswanathan M.
Title - Combination therapy of glibenclamide and insulin in NIDDM patients with secondary failure to oral drugs.

22. Authors - Bailey TS. Mezitis NH.
Title - Combination therapy with insulin and sulfonylureas for type II diabetes.
[Review] [49 refs]

23. Authors - Stenman S. Groop PH. Saloranta C. Totterman KJ. Fyhrqvist F. Groop L.
Title - Effects of the combination of insulin and glibenclamide in type 2 (non-insulin-dependent) diabetic patients with secondary failure to oral
hypoglycaemic agents.

Title - Trial of sulfonylurea in combination with insulin in the therapy of diabetes type I and II. Evidence against a primary extrapancreatic receptor effect.

2. Study outcomes don’t match (n = 43)

1. Authors - Guazzi M. Tumminello G. Matturri M. Guazzi MD.
Title - Insulin ameliorates exercise ventilatory efficiency and oxygen uptake in patients with heart failure-type 2 diabetes comorbidity.

Title - Effects of insulin lispro and chronic vitamin C therapy on postprandial lipaemia, oxidative stress and endothelial function in patients with type 2 diabetes mellitus.

3. Authors - Guldstrand M. Grill V. Bjorklund A. Lins PE. Adamson U.
Title - Improved beta cell function after short-term treatment with diazoxide in obese subjects with type 2 diabetes.

4. Authors - Guazzi M. Oreglia I. Guazzi MD.
Title - Insulin improves alveolar-capillary membrane gas conductance in type 2 diabetes.
5. Authors - Stefanidis A. Melidonis A. Tournis S. Zairis M. Handanis S. Olympios C. Asimacopoulos P. Foussas S.
Title - Intensive insulin treatment reduces transient ischaemic episodes during acute coronary events in diabetic patients.

6. Authors - Sreekumar R. Halvatsiotis P. Schimke JC. Nair KS.

7. Authors - Lindholm A. Jensen LB. Home PD. Raskin P. Boehm BO. Rastam J.
Title - Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes.

8. Authors - Karlvedt L. Andersson G. Efendic S. Grill V.
Title - A rapid increase in beta-cell function by multiple insulin injections in type 2 diabetic patients is not further enhanced by prolonging treatment.[comment].

Title - Effects of treatment with sulfonylurea drugs or insulin on ischemia-induced myocardial dysfunction in type 2 diabetes.
Source - Diabetes. 51(3):808-12, 2002 Mar.

10. Authors - Reza M. Taylor CD. Towse K. Ward JD. Hendra TJ.
Title - Insulin improves well-being for selected elderly type 2 diabetic subjects.
Title - Troglitazone but not metformin restores insulin-stimulated phosphoinositide 3-kinase activity and increases p110beta protein levels in skeletal muscle of type 2 diabetic subjects.
Source - Diabetes. 51(2):443-8, 2002 Feb.

12. Authors - Bagg W. Whalley GA. Gamble G. Drury PL. Sharpe N. Braatvedt GD.
Title - Effects of improved glycaemic control on endothelial function in patients with type 2 diabetes.

Title - Correction of hyperglycaemia reduces insulin resistance and serum soluble E-selectin levels in patients with Type 2 diabetes mellitus.

14. Authors - Ryysy L. Yki-Jarvinen H.
Title - Improvement of glycemic control by 1 year of insulin therapy leads to a sustained decrease in sE-selectin concentrations in type 2 diabetes.

15. Authors - Davis TM. Clifford RM. Davis WA. The Fremantle Diabetes Study.
Title - Effect of insulin therapy on quality of life in Type 2 diabetes mellitus: The Fremantle Diabetes Study.

16. Authors - Bastyr EJ 3rd. Huang Y. Brunelle RL. Vignati L. Cox DJ. Kotsanos JG.
Title - Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro.

17. Authors - Rivellese AA. Patti L. Romano G. Innelli F. Di Marino L. Annuzzi G. Iavicoli M. Coronel GA. Riccardi G.
Title - Effect of insulin and sulfonylurea therapy, at the same level of blood glucose control, on low density lipoprotein subfractions in type 2 diabetic patients.

18. Authors - Yudkin JS. Panahloo A. Stehouwer C. Emeis JJ. Bulmer K. Mohamed-Ali V. Denver AE.
Title - The influence of improved glycaemic control with insulin and sulphonylureas on acute phase and endothelial markers in Type II diabetic subjects.
Source - Diabetologia. 43(9):1099-106, 2000 Sep.

19. Authors - Levin SR. Coburn JW. Abaira C. Henderson WG. Colwell JA. Emanuele NV. Nuttall FQ. Sawin CT. Comstock JP. Silbert CK.
Title - Effect of intensive glycemic control on microalbuminuria in type 2 diabetes.
Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators.

20. Authors - Makimattila S. Nikkila K. Yki-Jarvinen H.
Institution - Department of Medicine, Helsinki University Central Hospital, Finland.
Title - Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus.

21. Authors - Yu JG. Kruszynska YT. Mulford MI. Olefsky JM.
Title - A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients.
Source - Diabetes. 48(12):2414-21, 1999 Dec.

22. Authors - Lindstrom T. Nystrom FH. Olsson AG. Ottosson AM. Arnqvist HJ.
Title - The lipoprotein profile differs during insulin treatment alone and combination therapy with insulin and sulphonylureas in patients with Type 2 diabetes mellitus.

23. Authors - Tovi J. Svanborg E. Nilsson BY. Engfeldt P.
Title - Diabetic neuropathy in elderly Type 2 diabetic patients: effects of insulin treatment.

Title - Effect of intensive glycemic control on fibrinogen, lipids, and lipoproteins: Veterans Affairs Cooperative Study in Type II Diabetes Mellitus.

25. Authors - van der Does FE. de Neeling JN. Snoek FJ. Grootenhuis PA. Kostense PJ. Bouter LM. Heine RJ.
Title - Randomized study of two different target levels of glycemic control within the acceptable range in type 2 diabetes. Effects on well-being at 1 year.

26. Authors - Duckworth WC. et al.
Title - The Veterans Affairs Implantable Insulin Pump Study: effect on cardiovascular risk factors.
27. Authors - Fonseca VA. Reynolds T. Hemphill D. Randolph C. Wall J. Valiquet TR. Graveline J. Fink LM.
Title - Effect of troglitazone on fibrinolysis and activated coagulation in patients with non-insulin-dependent diabetes mellitus.

28. Authors - Panahloo A. Mohamed-Ali V. Andres C. Denver AE. Yudkin JS.
Title - Effect of insulin versus sulfonylurea therapy on cardiovascular risk factors and fibrinolysis in type II diabetes.

29. Authors - Rachman J. Payne MJ. Levy JC. Barrow BA. Holman RR. Turner RC.
Title - Changes in amylin and amylin-like peptide concentrations and beta-cell function in response to sulfonylurea or insulin therapy in NIDDM.

30. Authors - Tovi J. Furhoff AK. Lennerhagen P. Engfeldt P.
Title - Starting insulin therapy in elderly non-insulin-dependent diabetic patients at a health care centre. Methodological and economic aspects.

31. Authors - Rodier M. Colette C. Gouzes C. Michel F. Crastes de Paulet A. Monnier L.
Title - Effects of insulin therapy upon plasma lipid fatty acids and platelet aggregation in NIDDM with secondary failure to oral antidiabetic agents.

32. Authors - Gibson JM. Westwood M. Crosby SR. Gordon C. Holly JM. Fraser W. Anderson C. White A. Young RJ.
Title - Choice of treatment affects plasma levels of insulin-like growth factor-binding protein-1 in noninsulin-dependent diabetes mellitus.
33. Authors - Dela F. Larsen JJ. Mikines KJ. Galbo H.
Title - Normal effect of insulin to stimulate leg blood flow in NIDDM.
Source - Diabetes. 44(2):221-6, 1995 Feb.

34. Authors - Malmberg KA. Efendic S. Ryden LE.
Title - Feasibility of insulin-glucose infusion in diabetic patients with acute myocardial infarction. A report from the multicenter trial: DIGAMI.
Source - Diabetes Care. 17(9): 1007-14, 1994 Sep.

35. Authors - Pregant P. Kaiser E. Schernthaner G.
Title - No effect of insulin treatment or glycemic improvement on plasma carnitine levels in type 2 diabetic patients.

Title - Mechanisms of arterial hypotension after therapeutic dose of subcutaneous insulin in diabetic autonomic neuropathy.

37. Authors Jain SK. Nagi DK. Slavin BM. Lumb PJ. Yudkin JS.
Title - Insulin therapy in type 2 diabetic subjects suppresses plasminogen activator inhibitor (PAI-1) activity and proinsulin-like molecules independently of glycaemic control.

38. Authors - Boyd K. Rogers C. Boreham C. Andrews WJ. Hadden DR.
Title - Insulin, glibenclamide or metformin treatment for non insulin dependent diabetes: heterogenous responses of standard measures of insulin action and insulin secretion before and after differing hypoglycaemic therapy.

Title - C-peptide profiles in patients with non-insulin-dependent diabetes mellitus before and during insulin treatment.

40. Authors - Peacock I. Watts R. Selby C. Tattersall RB.
Title - Serum C-peptide after 6 months on glibenclamide remains higher than during insulin treatment.

41. Authors - Firth R. Bell P. Marsh M. Rizza RA.
Title - Effects of tolazamide and exogenous insulin on pattern of postprandial carbohydrate metabolism in patients with non-insulin-dependent diabetes mellitus.
Results of randomized crossover trial.

42. Authors - Frazier LM. Mulrow CD. Alexander LT Jr. Harris RT. Heise KR. Brown JT. Feussner JR.
Title - Need for insulin therapy in type II diabetes mellitus. A randomized trial.

43. Authors - Diehl AK. Sugarek NJ. Bauer RL.
Title - Medication compliance in non-insulin-dependent diabetes: a randomized comparison of chlorpropamide and insulin.
3. Wrong patient group (n=1)

1. Authors - Gentile S. Turco S. Guarino G. Oliviero B. Annunziata S. Cozzolino D. Sasso FC. Turco A. Salvatore T. Torella R.
Title - Effect of treatment with acarbose and insulin in patients with non-insulin-dependent diabetes mellitus associated with non-alcoholic liver cirrhosis.

4. Insufficient patient numbers (n=13)

1. Authors - HO LT. Lam HC. Wu MS. Kwok CF. Jap TS. Tang KT. Wang LM. Liu YF.
Title - A twelve month double-blind randomized study of the efficacy and immunogenicity of human and porcine insulins in non-insulin-dependent diabetics.

2. Authors - Fritsche A. Schmulling RM. Haring HU. Stumvoll M.
Title - Intensive insulin therapy combined with metformin in obese type 2 diabetic patients.

Title - Insulin and sulfonylurea therapy in NIDDM patients. Are the effects on lipoprotein metabolism different even with similar blood glucose control?.

4. Authors - Rachman J. Levy JC. Barrow BA. Manley SE. Turner RC.
Title - Relative hyperproinsulinemia of NIDDM persists despite the reduction of hyperglycemia with insulin or sulfonylurea therapy.
5. Authors - Niskanen L. Lahti J. Uusitupa M.
Title - Morning or bed-time insulin with or without glibenclamide in elderly type 2 diabetic patients unresponsive to oral antidiabetic agents.

6. Authors - Sane T. Helve E. Yki-Jarvinen H. Taskinen MR.
Title - One-year response to evening insulin therapy in non-insulin-dependent diabetes.

7. Authors - Vigneri R. Trischitta V. Italia S. Mazzarino S. Rabuazzo MA. Squatrito S.
Title - Treatment of NIDDM patients with secondary failure to glyburide: comparison of the addition of either metformin or bed-time NPH insulin to glyburide.

8. Authors - HO LT. Lam HC. Wu MS. Kwok CF. Jap TS. Tang KT. Wang LM. Liu YF.
Title - A twelve month double-blind randomized study of the efficacy and immunogenicity of human and porcine insulins in non-insulin-dependent diabetics.

9. Authors - Winocour PH. Mallik TH. Ishola M. Baker RD. Bhatnagar D. Durrington PN. Anderson DC.
Title - A randomized cross-over study of the effects of proinsulin on lipid metabolism in type 2 diabetes.

10. Authors - Drexel H. Hopferwieser T. Braunsteiner H. Patsch JR.
Title - Effects of biosynthetic human proinsulin on plasma lipids in type 2 diabetes mellitus.
Title - Effects of hypocaloric diet and insulin therapy on metabolic control and mechanisms of hyperglycemia in obese non-insulin-dependent diabetic subjects.

12. Authors - Firth RG. Bell PM. Rizza RA.
Title - Effects of tolazamide and exogenous insulin on insulin action in patients with non-insulin-dependent diabetes mellitus.

13. Authors - Kyllastinen M. Groop L.
Title - Combination of insulin and glibenclamide in the treatment of elderly non-insulin dependent (type 2) diabetic patients.

5. Inadequate study treatment duration (n=4)

1. Authors - McSorley PT. Bell PM. Jacobsen LV. Kristensen A. Lindholm A.
Title - Twice-daily biphasic insulin aspart 30 versus biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus.

Title - Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes.

3. Authors - Malone JK. Yang H. Woodworth JR. Huang J. Campagne BN. Halle JP. Yale JF. Grossman LD.
Title - Humalog Mix25 offers better mealtime glycemic control in patients with type 1 or type 2 diabetes.

Title - Improved postprandial glycemic control with Humalog Mix75/25 after a standard test meal in patients with type 2 diabetes mellitus.

6. Duplicate study (or study participants) (n=15)

1. Authors - Boehm BO. Home PD. Behrend C. Kamp NM. Lindholm A.
Title - Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients.

Title - A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes.

3. Authors - Rosenstock J. Schwartz SL. Clark CM Jr. Park GD. Donley DW. Edwards MB.
Title - Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin.

4. Authors - Yki-Jarvinen H. Dressler A. Ziemen M. HOE 901/300s Study Group.
Title - Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime
insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group.
Source - Diabetes Care. 23(8):1130-6, 2000 Aug.

5. Authors - Azad N. Emanuele NV. Abraira C. Henderson WG. Colwell J. Levin SR. Nuttall FQ. Comstock JP. Sawin CT. Silbert C. Rubino FA.
Title - The effects of intensive glycemic control on neuropathy in the VA cooperative study on type II diabetes mellitus (VA CSDM).

6. Authors - UK Prospective Diabetes Study (UKPDS) Group.
Title - Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group.

7. Authors - Agrawal L. Emanuele NV. Abraira C. Henderson WG. Levin SR. Sawin CT. Silbert CK. Nuttall FQ. Comstock JP. Colwell JA.
Title - Ethnic differences in the glycemic response to exogenous insulin treatment in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM).

8. Authors - Schwartz S. Raskin P. Fonseca V. Graveline JF.
Title - Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. Troglitazone and Exogenous Insulin Study Group.

9. Authors - UK Prospective Diabetes Study (UKPDS) Group.
Title - United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled
trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group.

Title - Evaluations of retinopathy in the VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM). A feasibility study.

11. Authors - Colwell JA.
Title - The feasibility of intensive insulin management in non-insulin-dependent diabetes mellitus. Implications of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM.

12. Authors - UK Prospective Diabetes Study (UKPDS) Group.

Title - Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes.

14. Authors - UK Prospective Diabetes Study (UKPDS) Group.
Title - United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of
randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly
diagnosed non-insulin dependent diabetes followed for three years.

15. Authors - UK Prospective Diabetes Study (UKPDS) Group.
Title - U.K. prospective diabetes study. II. Reduction in HbA1c with basal insulin
supplement, sulfonylurea, or biguanide therapy in maturity-onset diabetes. A multicenter
study.

7. Irrelevant treatment comparison (n=20)

1. Authors - Ratner RE. Want LL. Fineman MS. Velte MJ. Ruggles JA. Gottlieb A.
Weyer C. Kolterman OG.
Title - Adjunctive therapy with the amylin analogue pramlintide leads to a combined
improvement in glycemic and weight control in insulin-treated subjects with type 2
diabetes.

2. Authors - Cappelleri JC. Cefalu WT. Rosenstock J. Kourides IA. Gerber RA.
Title - Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin
regimen and a subcutaneous insulin regimen.
Source - Clinical Therapeutics. 24(4):552-64, 2002 Apr.

3. Authors - Kelley DE. Bray GA. Pi-Sunyer FX. Klein S. Hill J. Miles J. Hollander P.
Title - Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-
treated type 2 diabetes: A 1-year randomized controlled trial.

4. Authors - Kelley DE. Bray GA. Pi-Sunyer FX. Klein S. Hill J. Miles J. Hollander P.
Title - Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial.

Title - Gemfibrozil improves insulin sensitivity and flow-mediated vasodilatation in type 2 diabetic patients.

6. Authors - Di Mauro M. Papalia G. Le Moli R. Nativo B. Nicoletti F. Lunetta M.
Title - Effect of octreotide on insulin requirement, hepatic glucose production, growth hormone, glucagon and c-peptide levels in type 2 diabetic patients with chronic renal failure or normal renal function.

7. Authors - Rustemeijer C. Schouten JA. Voerman HJ. Hensgens HE. Donker AJ. Heine RJ.
Title - Pravastatin compared to bezafibrate in the treatment of dyslipidemia in insulin-treated patients with type 2 diabetes mellitus.
Source - Diabetes/Metabolism Research Reviews. 16(2):82-7, 2000 Mar-Apr.

8. Authors - Cagliero E. Levina EV. Nathan DM.
Title - Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients.

9. Authors - de Valk HW. Verkaaik R. van Rijn HJ. Geerdink RA. Struyvenberg A.
Title - Oral magnesium supplementation in insulin-requiring Type 2 diabetic patients.
10. Authors - Thompson RG, Pearson L, Schoenfeld SL, Kolterman OG.
Title - Pramlintide, a synthetic analog of human amylin, improves the metabolic profile of patients with type 2 diabetes using insulin. The Pramlintide in Type 2 Diabetes Group.

Title - Added benfluorex in obese insulin-requiring type 2 diabetes.

Title - A long-term comparison between enalapril and captopril on insulin sensitivity in normotensive non-insulin dependent diabetic volunteers.

13. Authors - Jendle JH, Karlberg BE.
Title - Effects of intrapulmonary insulin in patients with non-insulin-dependent diabetes.

Title - A comparison of the effects of low- and conventional-dose thiazide diuretic on insulin action in hypertensive patients with NIDDM.

Title - 1,5-Anhydro-D-glucitol evaluates daily glycemic excursions in well-controlled NIDDM.
16. Authors - Brooks B. Cistulli PA. Borkman M. Ross G. McGhee S. Grunstein RR. Sullivan CE. Yue DK.
Title - Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness.

17. Authors - Willey KA. Molyneaux LM. Yue DK.
Title - Obese patients with type 2 diabetes poorly controlled by insulin and metformin: effects of adjunctive dexfenfluramine therapy on glycaemic control.

18. Authors - Paolisso G. D'Amore A. Giugliano D. Ceriello A. Varricchio M. D'Onofrio F.
Title - Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients.

19. Authors - Larkins RG. Zajac J. Saunders R. Read A. Hopper JL.
Title - Comparative double-blind trial of the effectiveness and antigenicity of semisynthetic human insulin and purified porcine insulin in newly treated diabetic subjects.

20. Authors - Moffitt PS. Colagiuri S. Miller JJ. Hall CA.
Appendix 5: EMBASE Eligible Studies after title and abstract review
(n=18)

The EMBASE search yielded a total of 185 studies. After reviewing all titles and abstracts 18 were considered eligible for further evaluation.

1. Authors - Sargin H. Sargin M. Altuntas Y. Sengul AM. Orbay E. Seber S. Ucak S. Yayla A.
Title - Comparison of lunch and bedtime NPH insulin plus mealtime insulin Lispro therapy with premeal regular insulin plus bedtime NPH insulin therapy in type 2 diabetes.

2. Authors - Raskin P. Bode BW. Marks JB. Hirsch IB. Weinstein RL. McGill JB. Peterson GE. Mudaliar SR. Reinhardt RR.
Title - Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: A randomized, parallel-group, 24-week study.

3. Authors - Schwartz S. Sievers R. Strange P. Lyness WH. Hollander P.
Title - Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: Efficacy, safety, and cost analysis.

Title - Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients.

5. Authors - Hwu C-M. Ho L-T. Fuh MMT. Siu SC. Sutanegara D. Piliang S. Chan JCN.
Title - Acarbose improves glycemic control in insulin-treated Asian type 2 diabetic patients: Results from a multinational, placebo-controlled study.
6. Authors - Stehouwer MHA. DeVries JH. Lumeij JAE. Ader HJ. Engbers AMS. van Iperen A. Snoek FJ. Heine RJ.
Title - Combined bedtime insulin - Daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: Effects on HbA1c and hypoglycaemia rate - A randomised trial.

Title - Efficacy and safety of acarbose in insulin-treated patients with type 2 diabetes.

8. Authors - Robinson AC. Burke J. Robinson S. Johnston DG. Elkeles RS.
Title - The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control.

9. Authors - Riddle MC. Schneider J.
Title - Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone.

10. Authors - Feinglos MN. Thacker CR. Lobaugh B. DeAtkine DD. McNeill DB. English JS. Bursey DL.
Title - Combination insulin and sulfonylurea therapy in insulin-requiring type 2 diabetes mellitus.
11. Authors - Anderson JH Jr. et al  
Title - Improved mealtime treatment of diabetes mellitus using an insulin analogue.  

12. Authors - Saudek CD. Et al  
Title - Implantable insulin pump vs multiple-dose insulin for non-insulin- dependent diabetes mellitus: A randomized clinical trial.  

13. Authors - Clauson P. Karlander S. Steen L. Efendic S.  
Title - Daytime glibenclamide and bedtime NPH insulin compared to intensive insulin treatment in secondary sulphonylurea failure: A 1-year follow-up.  

Title - A long-term, randomized, comparative study of insulin versus sulfonylurea therapy in type 2 diabetes.  

15. Authors - Taylor R. Foster B. Kyne-Grzebalski D. Vanderpump M.  
Title - Insulin regimens for the non-insulin dependent: Impact on diurnal metabolic state and quality of life.  

Title - Metformin for obese, insulin-treated diabetic patients: Improvement in glycaemic control and reduction of metabolic risk factors.  
17. Authors - Riddle MC, Hart JS, Bouma DJ, Phillipson BE, Youker G.
Title - Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetic subjects.

18. Authors - Tindall H, Bodansky HJ, Stickland M, Wales JK.
Title - A strategy for selection of elderly Type 2 diabetic patients for insulin therapy, and a comparison of two insulin preparations.
Appendix 6: EMBASE Excluded Studies after title and abstract review
(n=167)

Out of 185 studies yielded by the EMBASE search, 167 were considered ineligible for inclusion in the systematic review. All the excluded studies have been grouped below according to reason for exclusion.

1. Not a randomised controlled trial (n=44)

1. Authors - Delea TE. Edelsberg JS. Hagiwara M. Oster G. Phillips LS.
   Title - Use of Thiazolidinediones and Risk of Heart Failure in People With Type 2 Diabetes: A retrospective cohort study.

2. Authors - Murata GH. Shah JH. Wendel CS. Hoffman RM. Adam KD. Bokhari SU.
   Solvas PA. Duckworth WC.
   Title - Risk factor management in stable, insulin-treated patients with Type 2 diabetes: The Diabetes Outcomes in Veterans Study.

3. Authors - Lteif AA. Mather KJ. Clark CM.
   Title - Diabetes and heart disease: An evidence-driven guide to risk factors management in diabetes.

4. Authors - Gadsby R.
   Title - Using insulin earlier in the treatment of type 2 diabetes.

5. Authors - Barnett AH. Capaldi B. Davis-Lyons M. Farooqi A. Gadsby R. Gilroy J. Hill J. Hughes E. Kirby M. Owens D. Tasker PRW. Vora J.
Title - Expert opinion statement on the use of insulin therapy in patients with type 2 diabetes in primary care.

6. Authors - Home PD. Boulton AJM. Jimenez J. Landgraf R. Osterbrink B. Christiansen JS.
Title - Issues relating to the early or earlier use of insulin in type 2 diabetes.

7. Authors - Yki-Jarvinen H.
Title - Combination therapy with insulin and oral agents: Optimizing glycemic control in patients with type 2 diabetes mellitus.

8. Authors - Scherbaum WA.
Title - Insulin therapy in Europe.

9. Authors - Riddle MC.
Title - The underuse of insulin therapy in North America.

10. Authors - Bouldin MJ. Low AK. Blackston JW. Duddlestone DN. Holman HE. Hicks GS. Brown CA.
Title - Quality of care in diabetes: Understanding the guidelines.

11. Authors - Tong PC. Chow CC. Jorgensen LN. Cockram CS.
Title - The contribution of metformin to glycaemic control in patients with Type 2 diabetes mellitus receiving combination therapy with insulin.

12. Authors - Still JG.
Title - Development of oral insulin: Progress and current status.

13. Authors - Kanoun F. Amor ZB. Zouari B. Khalifa FB.
Title - Insulin therapy may increase blood pressure levels in type 2 diabetes mellitus.

14. Authors - Mudaliar S. Edelman SV.
Title - Insulin therapy in type 2 diabetes.

15. Authors - Camacho P. Pitale S. Abraira C.
Title - Beneficial and detrimental effects of intensive glycaemic control, with emphasis on type 2 diabetes mellitus.

16. Authors - Yki-Jarvinen H.
Title - Comparison of insulin regimens for patients with type 2.

17. Authors - Buse J.
Title - Combining insulin and oral agents.
18. Authors - Davidson JA. Garber AJ. Guthrie RA. Stoltje PA.
Title - Type 2 diabetes: Earlier detection, younger patients.

19. Authors - Fonseca V. Foyt HL. Shen K. Whitcomb R.
Title - Long-term effects of troglitazone: Open-label extension studies in type 2 diabetic patients.

20. Authors - Laakso M.
Title - Hyperglycemia as a risk factor for cardiovascular disease in type 2 diabetes.
Source - Primary Care; Clinics in Office Practice. Vol. 26(4)(pp 829-839), 1999.

21. Authors - DeFronzo RA.
Title - Pharmacologic therapy for type 2 diabetes mellitus.

22. Authors - Turner RC.
Title - The U.K. Prospective Diabetes Study: A review.

23. Authors - Scheen AJ.
Title - Clinical efficacy of acarbose in diabetes mellitus: A critical review of controlled trials.

24. Authors - Granberry MC. Schneider EE. Fonseca VA.
Title - The role of troglitazone in treating the insulin resistance syndrome.

25. Authors - Raskin P.
Title - Rethinking the use of oral agents in the treatment of type 2 diabetes mellitus.

26. Authors - Gaster B. Hirsch IB.
Title - The effects of improved glycemic control on complications in type 2 diabetes.

27. Authors - Purnell JQ. Hirsch IB.
Title - New oral therapies for type 2 diabetes.

28. Authors - Garancini MP. Gallus G. Cucinotta D. Rossi A. Riccardi G.
Title - Factors related to glycemic control in IDDM and insulin-treated NIDDM patients in current practice: A comparison of care policies.

29. Authors – Henry RR.
Title - Thiazolidinediones.

30. Authors - Chlup R. Vaverkova H. Bartek J.
Title - Complementary insulin therapy improves blood glucose and serum lipid parameters in type 2 (non-insulin-dependent) diabetic patients. I. Effects on blood glucose control.

31. Authors - Vercaigne LM.
Title - Another step forward in the management of diabetes mellitus.
32. Authors - Saltiel AR. Olefsky JM.
Title - Thiazolidinediones in the treatment of insulin resistance and type II diabetes.

33. Authors - Goo AKY. Carson DS. Bjelajac A.
Title - Metformin: A new treatment option for non-insulin-dependent diabetes mellitus.

34. Authors - Johnson JL. Wolf SL. Kabadi UM.
Title - Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: A meta-analysis of the randomized placebo-controlled trials.

35. Authors - Levy J. Vandenber M. Grunberger G.
Title - Insulin versus glipizide treatment in patients with non-insulin-dependent diabetes mellitus. Effects on blood pressure and glucose tolerance.

36. Authors - Kuusi T. et al
Title - Effect of insulin treatment on serum lipoprotein(a) in non-insulin-dependent diabetes.

37. Authors - Knowler WC. Narayan KMV.
Title - Prevention of non-insulin-dependent diabetes mellitus.

38. Authors - Niskanen L. Enlund H. Jormanainen V. Nissineu A. Uusitupa M.
Title - Therapeutic traditions in type 2 diabetes - Are they changing?.

39. Authors - Janatuinen E. Pikkarainen P. Laakso M. Pyorala K.
Title - Gastrointestinal symptoms in middle-aged diabetic patients.

40. Authors - Pugh JA. Wagner ML. Sawyer J. Ramirez G. Tuley M. Friedberg SJ.
Title - Is combination sulfonylurea and insulin therapy useful in NIDDM patients: A metaanalysis.

41. Authors - Peters AL. Davidson MB.
Title - Insulin plus a sulfonylurea agent for treating type 2 diabetes.

42. Authors - Liu D. Wettergren M. Lins P-E. Adamson U.
Title - Combined insulin-glibenclamide therapy of NIDDM patients in primary health care. A follow-up study of its compliance and efficacy and a review of the literature.

43. Authors - Bailey TS. Mezitis NHE.
Title - Combination therapy with insulin and sulfonylureas for type II diabetes.

44. Authors - Simpson HCR. Sturley R. Stirling CA. Reckless JPD.
Title - Combination of insulin with glipizide increases peripheral glucose disposal in secondary failure Type 2 diabetic patients.

2. Study outcomes don’t match (n = 22)
1. Authors - Purnell JQ. Dev RK. Steffes MW. Cleary PA. Palmer JP. Hirsch IB. Hokanson JE. Brunzell JD.
Title - Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the diabetes control and complications trial.

2. Authors - Schafers RF.
Title - Do effects on blood pressure contribute to improved clinical outcomes with metformin?.

3. Authors - Takino H. et al
Title - Antibodies to GAD in Japanese patients classified as Type 2 diabetes at diagnosis. High titre of GAD Ab is a predictive marker for early insulin treatment - Report of west Japan (Kyushu, Yamaguchi, Osaka) study for GAD Ab(+) diabetes.

4. Authors - Taylor C. Towe K. Reza M. Ward JD. Hendra TJ.
Title - Transferring elderly type 2 patients to insulin: A prospective study of diabetes nurses', physicians' and patients' perceptions.

5. Authors - De Grauw WJC. Van De Lisdonk EH. Van Gerwen WHEM. Van Den Hoogen HJM. Van Weel C.
Title - Insulin therapy in poorly controlled type 2 diabetic patients: Does it affect quality of life?.

6. Authors - Szabo Z. Arnqvist H. Hakanson E. Jorfeldt L. Svedjeholm R.
Title - Effects of high-dose glucose-insulin-potassium on myocardial metabolism after coronary surgery in patients with type II diabetes.

7. Authors - Hemmerling TM. Schmid MC. Schmidt J. Kern S. Jacobi KE.
Title - Comparison of a continuous glucose-insulin-potassium infusion versus intermittent bolus application of insulin on perioperative glucose control and hormone status in insulin-treated type 2 diabetics.

Title - Role of free fatty acids on cardiac autonomic nervous system in noninsulin-dependent diabetic patients: Effects of metabolic control.

9. Authors - Laedtke T. Kjems L. Porksen N. Schmitz O. Veldhuis J. Kao PC. Butler PC.
Title - Overnight inhibition of insulin secretion restores pulsatility and proinsulin/insulin ratio in type 2 diabetes.

10. Authors - Wake N. Hisashige A. Katayama T. Kishikawa H. Ohkubo Y. Sakai M. Araki E. Shichiri M.
Title - Cost-effectiveness of intensive insulin therapy for type 2 diabetes: A 10-year follow-up of the Kumamoto study.

12. Authors - Fanghanel G. Silva U. Sanchez-Reyes L. Sisson D. Sotres D. Torres EM.
Title - Effects of metformin on fibrinogen levels in obese patients with type 2 diabetes.

13. Authors - Tovi J. Engfeldt P.
Title - Well-being and symptoms in elderly Type 2 diabetes patients with poor metabolic control: Effect of insulin treatment.

Title - Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus.

15. Authors - Van der Wal PS. Draeger KE. Van Iperen AM. Martini C. Aarsen M. Heine RJ.
Title - Beta cell response to oral glimepiride administration during and following a hyperglycaemic clamp in NIDDM patients.

16. Authors - Towner D. Kjos SL. Leung B. Montoro MM. Xiang A. Mestman JH. Buchanan TA.
Title - Congenital malformations pregnancies complicated by NIDDM: Increased risk from poor maternal metabolic control but not from exposure to sulfonylurea drugs.

17. Authors - Paolisso G. D'Amore A. Giugliano D. Ceriello A. Varricchio M. D'Onofrio F.
Title - Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients.

18. Authors - Lindstrom T. Arnqvist HJ. Ludvigsson J. Von Schenck HH.
Title - C-peptide profiles in patients with non-insulin-dependent diabetes mellitus before and during insulin treatment.

19. Authors - Winocour PH. Mallik TH. Ishola M. Baker RD. Bhatnagar D. Durrington PN. Anderson DC.
Title - A randomized cross-over study of the effects of proinsulin on lipid metabolism in Type 2 diabetes.

20. Authors - Sotaniemi EA. Vierimaa E. Huupponen R. Karvonen I. Vuoti MJ. Rytomaa K.
Title - Insulin and sulphonylurea in the therapy of type 2 diabetes.

21. Authors - Mayou R. Bryant B. Turner R.
Title - Quality of life in non-insulin-dependent diabetes and a comparison with insulin-dependent diabetes.
22. Authors - Sotaniemi EA. Karvonen I.
Title - Glucose tolerance and insulin response to glucose load before and after enzyme inducing therapy in subjects with glucose intolerance and patients with NIDDM having hyperinsulinemia or relative insulin deficiency.

3. Wrong patient group (n=1)

1. Authors - Schultz CJ. Neil HAW. Dalton RN. Bahu TK. Dunger DB.
Title - Blood pressure does not rise before the onset of microalbuminuria in children followed from diagnosis of type 1 diabetes.

4. Insufficient patient numbers (n=11)

1. Authors - Kabadi MU. Kabadi UM.
Title - Efficacy of Sulfonylureas with Insulin in Type 2 Diabetes Mellitus.

2. Authors - Olsson PO. Lindstrom T.
Title - Combination-therapy with bedtime NPH insulin and sulphonylureas gives similar glycaemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes.

Title - Insulin and sulfonylurea therapy in NIDDM patients: Are the effects on lipoprotein metabolism different even with similar blood glucose control?.
4. Authors - Bagdade JD. Kelley DE. Henry RR. Eckel RH. Ritter MC.
Title - Effects of multiple daily insulin injections and intraperitoneal insulin therapy on cholesteryl ester transfer and lipoprotein lipase activities in NIDDM.

5. Authors - Rodier M. Colette C. Gouzes C. Michel F. Crastes de Paulet A. Monnier L.
Title - Effects of insulin therapy upon plasma lipid fatty acids and platelet aggregation in NIDDM with secondary failure to oral antidiabetic agents.

6. Authors - Niskanen L. Lahti J. Uusitupa M.
Title - Morning or bed-time insulin with or without glibenclamide in elderly Type 2 diabetic patients unresponsive to oral antidiabetic agents.

7. Authors - Karlander SG. Gutniak MKM. Efendic S.
Title - Effects of combination therapy with glyburide and insulin on serum lipid levels in NIDDM patients with secondary sulfonylurea failure.

8. Authors - Blackshear PJ. Roussell AM. Cohen AM. Nathan DM.
Title - Basal-rate intravenous insulin infusion compared to conventional insulin treatment in patients with type II diabetes. A prospective crossover trial.

9. Authors - Wolffenbuttel BHR. Weber RFA. Van Koetsveld PM. Weeks L. Verschoor L.
Title - A randomized crossover study of sulphonylurea and insulin treatment in patients with Type 2 diabetes poorly controlled on dietary therapy.

10. Authors - Stenman S. Groop P-H. Saloranta C. Totterman KJ. Fyhrqvist F. Groop L.
Title - Effects of the combination of insulin and glibenclamide in Type 2 (non-insulin-dependent) diabetic patients with secondary failure to oral hypoglycaemic agents.

11. Authors - Lins P-E. Lundblad S. Persson-Trotzig E. Adamson U.
Title - Glibenclamide improves the response to insulin treatment in non-insulin-dependent diabetics with second failure to sulfonylurea therapy.

5. Inadequate study treatment duration (n=3)

1. Authors - Gonzalez-Michaca L. Ahumada M. Ponce-de-Leon S.
Title - Insulin subcutaneous application vs. continuous infusion for postoperative blood glucose control in patients with non-insulin-dependent diabetes mellitus.

Title - Insulin treatment regimen for Type II (non-insulin dependent) diabetes mellitus as judged by residual B-cell function.

3. Authors - Mailing B. Knudsen L. Christiansen CL. Schurizek BA. Alberti KGMM. Hermansen K.
Title - Insulin treatment in non-insulin dependent diabetic patients undergoing minor surgery.
Source - Diabetes, Nutrition & Metabolism - Clinical & Experimental. Vol. 2(2)(pp
6. Duplicate study (or study participants) (n=46)

1. Duplicate Medline Citation 6

2. Duplicate of Medline Citation 1.

3. Duplicate of Medline Citation 7

4. Duplicate of Medline Citation 29

5. Duplicate of Medline Citation 35

6. Duplicate of Medline Citation 31

7. Duplicate of Medline Citation 14

8. Duplicate of Medline Citation 13

9. Duplicate of Medline Citation 43

10. Duplicate of Medline Citation 40

11. Duplicate of Medline Citation 50

12. Duplicate of Medline Citation 54

13. Duplicate of Medline Citation 55

14. Duplicate of Medline Citation 91

15. Duplicate of Medline Citation 58

16. Duplicate of Medline Citation 70

17. Duplicate of Medline Citation 65

18. Duplicate of Medline Citation 68

19. Duplicate of Medline Citation 66

20. Duplicate of Medline Citation 75

21. Duplicate of Medline Citation 76

22. Duplicate of Medline Citation 77

23. Duplicate of Medline Citation 81

24. Duplicate of Medline Citation 16

25. Duplicate of Medline Citation 89

26. Duplicate of Medline Citation 91

27. Duplicate of Medline Citation 92

28. Duplicate of Medline Citation 93

29. Duplicate of Medline Citation 95
30. Duplicate of Embase Citation 103

31. Duplicate of Medline Citation 99

32. Duplicate of Medline Citation 101

33. Duplicate of Medline Citation 108

34. Duplicate of Medline Citation 91

35. Duplicate of Medline Citation 16

36. Duplicate of Medline Citation 113

37. Duplicate of Medline Citation 91

38. Duplicate of Medline Citation 118

39. Duplicate of Medline Citation 119

40. Duplicate of Medline Citation 16

41. Duplicate of Medline Citation 135

42. Duplicate of Medline Citation 16

43. Duplicate of Medline Citation 139

44. Duplicate of Medline Citation 144

45. Duplicate of Medline Citation 153
7. Irrelevant treatment comparison (n=40)

   Title - Addition of pramlintide to insulin therapy lowers HbA1c in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets.

2. Authors - Weiss SR. Cheng S-L. Kourides IA. Gelfand RA. Landschulz WH.
   Title - Inhaled Insulin Provides Improved Glycemic Control in Patients With Type 2 Diabetes Mellitus Inadequately Controlled With Oral Agents: A Randomized Controlled Trial.

3. Authors - Bachmann W. Petzinna D. Raptis SA. Wascher T. Westermeier T.
   Title - Long-Term Improvement of Metabolic Control by Acarbose in Type 2 Diabetes Patients Poorly Controlled with Maximum Sulfonylurea Therapy.

4. Authors - Hollander PA. Levy P. Fineman MS. Maggs DG. Shen LZ. Strobel SA. Weyer C. Kolterman OG.
   Title - Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: A 1-year randomized controlled trial.

5. Authors - Kipnes M. Dandona P. Tripathy D. Still JG. Kosutic G.
Title - Control of postprandial plasma glucose by an oral insulin product (HIM2) in patients with type 2 diabetes.

6. Authors - Jones TA. Sautter M. Van Gaal LF. Jones NP.
Title - Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes.

7. Authors - Fox C. McKinnon C. Wall A. Lawton SA.
Title - Ability to handle, and patient preference for, insulin delivery devices in visually impaired patients with type 2 diabetes.

8. Authors - Whitelaw DC. Smith JM. Nattrass M.
Title - Effects of gemfibrozil on insulin resistance to fat metabolism in subjects with type 2 diabetes and hypertriglyceridaemia.

9. Authors - Park S. Choi SB.
Title - Effects of a-tocopherol supplementation and continuous subcutaneous insulin infusion on oxidative stress in Korean patients with type 2 diabetes.

10. Authors - Hanefeld M. Haffner SM. Menschikowski M. Koehler C. Temelkova-Kurktschiev T. Wildbrett J. Fischer S.
Title - Different effects of acarbose and glibenclamide on proinsulin and insulin profiles in people with Type 2 diabetes.
Title - Efficacy and tolerance of intranasal insulin administered during 4 months in severely hyperglycaemic Type 2 diabetic patients with oral drug failure: A cross-over study.

12. Authors - Heinemann L. Pfutzner A. Heise T.
Title - Alternative routes of administration as an approach to improve insulin therapy: Update on dermal, oral, nasal and pulmonary insulin delivery.

13. Authors - Cefalu WT. Skyler JS. Kourides IA. Landschulz WH. Balagtas CC. Cheng S-L. Gelfand RA.
Title - Inhaled human insulin treatment in patients with type 2 diabetes mellitus.

Title - Effect of pinitol treatment on insulin action in subjects with insulin resistance.

15. Authors - Nicholson AS. Sklar M. Barnard ND. Gore S. Sullivan R. Browning S.
Title - Toward improved management of NIDDM: A randomized, controlled, pilot intervention using a lowfat, vegetarian diet.

16. Authors - Redmon JB. Raatz SK. Kwong CA. Swanson JE. Thomas W. Bantle JE.
Title - Pharmacologic induction of weight loss to treat type 2 diabetes.
Title - Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents.

18. Authors - Mitrakou A. Tountas N. Raptis AE. Bauer RJ. Schulz H. Raptis SA.
Title - Long-term effectiveness of a new alpha-glucosidase inhibitor (BAY m1099-miglitol) in insulin-treated type 2 diabetes mellitus.

19. Authors - Polo V. Saibene A. Pontiroli AE.
Title - Nicotinamide improves insulin secretion and metabolic control in lean type 2 diabetic patients with secondary failure to sulphonylureas.

20. Authors - Hoffmann J. Spengler M.
Title - Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: The essen-II study.

21. Authors - Ahmad J. Siddiqui MA. Ahmad H.
Title - Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria.

22. Authors - Dunger DB. Acerini CL.
Title - Does recombinant human insulin-like growth factor-1 have a role in the treatment of diabetes?
23. Authors - Thompson RG. Gottlieb A. Organ K. Koda J. Kisicki J. Kolterman OG.
Title - Pramlintide: A human amylin analogue reduced postprandial plasma glucose, insulin, and C-peptide concentrations in patients with Type 2 diabetes.

Title - The safety of injecting insulin through clothing.

25. Authors - Jendle JH. Karlberg BE.
Title - Effects of intrapulmonary insulin in patients with non-insulin-dependent diabetes.

26. Authors - Pontiroli AE. Pacchioni M. Piatti PM. Cassisa C. Camisasca R. Pozza G.
Title - Benfluorex in obese noninsulin dependent diabetes mellitus patients poorly controlled by insulin: A double blind study versus placebo.

27. Authors - Bianchi R. De Vries DE. Bravenboer B. Erkelens DW.
Title - Effect of benfluorex in addition to insulin therapy in obese type II diabetic patients with secondary failure to conventional oral treatment.

28. Authors - Raucoules-Aime M. Labib Y. Levraut J. Gastaud P. Dolisi C. Grimaud D.
Title - Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery.
Title - Cost-effectiveness of medical nutrition therapy provided by dietitians for persons with non-insulin-dependent diabetes mellitus.

30. Authors - Franz MJ. Monk A. Barry B. McClain K. Weaver T. Cooper N. Upham P. Bergenstal R. Mazze RS.
Title - Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: A randomized, controlled clinical trial.

31. Authors - Coates PA. Ismail IS. Luzio SD. Griffiths I. Ollerton RL. Volund A. Owens DR.
Title - Intranasal insulin: The effects of three dose regimens on postprandial glycaemic profiles in type II diabetic subjects.

32. Authors - Morgan WA. Raskin P. Rosenstock J.
Title - A comparison of fish oil or corn oil supplements in hyperlipidemic subjects with NIDDM.

33. Authors - Brooks B. Cistulli PA. Borkman M. Ross G. McGhee S. Grunstein RR. Sullivan CE. Yue DK.
Title - Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: Effect of continuous positive airway pressure treatment on insulin responsiveness.
34. Authors - Willey KA. Molyneaux LM. Yue DK.
Title - Obese patients with Type 2 diabetes poorly controlled by insulin and metformin: Effects of adjunctive dexfenfluramine therapy on glycaemic control.

35. Authors - Nielsen S. Schmitz O. Moller N. Porksén N. Klausen IC. Alberti KGMM. Mogensen CE.
Title - Renal function and insulin sensitivity during simvastatin treatment in Type 2 (non-insulin-dependent) diabetic patients with microalbuminuria.

36. Authors - Laager R. Keller U.
Title - Effects of recombinant human insulin-like growth factor I and insulin on counterregulation during acute plasma glucose decrements in normal and Type 2 (non-insulin-dependent) diabetes subjects.

37. Authors - Laube BL. Georgopoulos A. Adams III GK.
Title - Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients.

38. Authors - Coscelli C. Calabrese G. Fedele D. Pisu E. Calderini C. Bistoni S. Lapolla A. Mauri MG. Rossi A. Zappella A.
Title - Use of premixed insulin among the elderly: Reduction of errors in patient preparation of mixtures.

39. Authors - Bruce DG. Chisholm DJ. Storlien LH. Borkman M. Kraegen EW.
Title - Meal-time intranasal insulin delivery in Type 2 diabetes.

40. Authors - Quatraro A. Consoli G. Magno M. Caretta F. Nardozza A. Ceriello A. Giugliano D.
Title - Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug?
December 12, 2003

Eli Lilly & Co Ltd

Dextra Court, Chapel Hill

Basingstoke, Hants RG21 5SY

Dear Sir/Madam,

I am writing to request your assistance with a research project. I am a Medical Registrar at Prince of Wales Hospital, Sydney. I am currently studying toward a Master of Science in Pharmaceutical Medicine at the University of Surrey, UK. As part of the course requirements I am undertaking a dissertation consisting of a systematic review of the use of insulin in type 2 diabetes mellitus. My aim is to establish what evidence exists supporting the use of various formulations/regimes and what is the best way of combining insulin with oral hypoglycaemic agents.

As you are among the market leaders in this therapeutic area, I am writing to seek your assistance in identifying trials conducted in this area. I am particularly interested in obtaining any trial data that you may have that is unpublished, but would also be thankful for your guidance in referring to me to what you may consider the most significant trials.

I am happy to receive correspondence either via post to my home address or electronically at kiernanhughes@hotmail.com.

Many thanks for your assistance in this regard.

Sincerely,

Dr Kiernan Hughes

E-mail - kiernanhughes@hotmail.com
Appendix 8: Pharmaceutical companies contacted with request for unpublished trial data

- Eli Lilly Australia Pty Ltd (Aust)
  112 Wharf road
  West Ryde NSW 2114

- Eli Lilly & Co Ltd (UK)
  Dextra Court, Chapel Hill
  Basingstoke, Hants RG21 5SY

- Aventis Pharma Ltd, (UK) Aventis House,
  50 Kings Hill Av, Kings Hill,
  West Malling Kent ME19 4AH

- Aventis Pharma Pty Ltd (Aust)
  27 Sirius Road
  Lane Cove NSW 2066

- Novo Nordisk Pharmaceuticals Pty Ltd (Aust)
  PO Box 7586
  Baulkam Hills NSW 2153

- Novo Nordisk Ltd (UK)
  Broadfield Park, Brighton Rd,
  Crawley, West Sussex RH11 9RT
Appendix 9:
Final list of eligible studies for inclusion in final review (n=88)
References for pp92-122

Of the 95 studies considered eligible after title and abstract review, 7 were excluded after in depth review of the full publications revealed major quality issues or other factors that meant they didn’t meet criteria for inclusion in the final analysis. A total of 88 studies were therefore included in the final analysis.

1. Authors - HOE 901/2004 Study Investigators Group.
   Title - Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients.

   Title - Combination of insulin and metformin in the treatment of type 2 diabetes.

3. Authors - Herz M. Arora V. Campagne BN. Scholtz HE. Potgieter MA. Mollentze W.
   Title - Humalog Mix25 improves 24-hour plasma glucose profiles compared with the human insulin mixture 30/70 in patients with type 2 diabetes mellitus.

4. Authors - Strowig SM. Aviles-Santa ML. Raskin P.
   Title - Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes.

5. Authors - Herz M. Profozic V. Arora V. Smircic-Duvnjak L. Kovacevic I. Boras J. Campagne BN. Metelko Z.
Title - Effects of a fixed mixture of 25% insulin lispro and 75% NPL on plasma glucose during and after moderate physical exercise in patients with type 2 diabetes.  

6. Authors- UK Prospective Diabetes Study (UKPDS) Group.  
Title - Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group.  

7. Authors - Turner RC. Cull CA. Frighi V. Holman RR.  
Title - Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group.  

# UKPDS 33 and UKPDS 49 utilise the same study participants and will be considered as one study for the purpose of any meta-analysis conducted. I have included them both as they provide different relevant data.

8. Authors - Schwartz S. Raskin P. Fonseca V. Graveline JF.  
Institution - Diabetes and Glandular Diseases Clinic, San Antonio, Tex., USA.  
Title - Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. Troglitazone and Exogenous Insulin Study Group.  

Title - A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes.  
10. Authors - Rosenstock J. Schwartz SL. Clark CM Jr. Park GD. Donley DW. Edwards MB.
Title - Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin.

11. Authors - Yki-Jarvinen H. Dressler A. Ziemen M. HOE 901/300s Study Group.
Title - Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group.
Source - Diabetes Care. 23(8): 1130-6, 2000 Aug.

12. Authors - Boehm BO. Home PD. Behrend C. Kamp NM. Lindholm A.
Institution - Universitatsklinikum Ulm, Ulm, Germany. bernhardm@medizin.uni-ulm.de
Title - Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients.

13. Authors - Zargar AH. Masoodi SR. Laway BA. Wani AI. Bashir MI.
Title - Response of regimens of insulin therapy in type 2 diabetes mellitus subjects with secondary failure.

Title - Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy.
15. Authors - Herz M. Sun B. Milicevic Z. Erickson P. Fovenyi J. Grzywa M. Pelikanova T.
Title - Comparative efficacy of preprandial or postprandial Humalog Mix75/25 versus glyburide in patients 60 to 80 years of age with type 2 diabetes mellitus.

Title - Long-term glycaemic improvement after addition of metformin to insulin in insulin-treated obese type 2 diabetes patients.
Source - Diabetes, Obesity & Metabolism. 3(6):428-34, 2001 Dec.

Title - A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents.

Title - Glycemic control with Humalog Mix25 in type 2 diabetes inadequately controlled with glyburide.

19. Authors - Ponsen HH. Elte JW. Lehert P. Schouten JP. Bets D.
Title - Combined metformin and insulin therapy for patients with type 2 diabetes mellitus.

20. Authors - Guvener N. Gedik O.
Title - Effects of combination of insulin and acarbose compared with insulin and
gliclazide in type 2 diabetic patients.

21. Authors - Aviles-Santa L, Sinding J, Raskin P.
Title - Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial.

22. Authors - Standl E, Baumgartl HJ, Fuchtenbusch M, Stemplinger J.
Title - Effect of acarbose on additional insulin therapy in type 2 diabetic patients with late failure of sulphonylurea therapy.

23. Authors - Abraira C, Henderson WG, Colwell JA, Nuttall FQ, Comstock JP, Emanuele NV, Levin SR, Sawin CT, Silbert CK.
Title - Response to intensive therapy steps and to glipizide dose in combination with insulin in type 2 diabetes. VA feasibility study on glycemic control and complications (VA CSDM).

24. Authors - Niazi R, Muzaffar Z.
Title - Comparison of bedtime NPH insulin or metformin combined with glibenclamide in secondary sulphonylurea failure in obese type II (NIDDM) patients.

25. Authors - Tovi J, Ingemansson SO, Engfeldt P.
Title - Insulin treatment of elderly type 2 diabetic patients: effects on retinopathy.

Title - Adding metformin versus insulin dose increase in insulin-treated but poorly controlled Type 2 diabetes mellitus: an open-label randomized trial.
27. Authors - Buse JB. Gumbiner B. Mathias NP. Nelson DM. Faja BW. Whitcomb RW.
Title - Troglitazone use in insulin-treated type 2 diabetic patients. The Troglitazone Insulin Study Group.

28. Authors - Penfornis A. Millot L.
Title - Initiating insulin treatment in insulin-requiring type 2 diabetic patients: comparative efficiency and cost of outpatient and inpatient management. INNOV Study Group.

29. Authors - Birkeland KI. Rishaug U. Hanssen KF. Vaaler S.
Title - NIDDM: a rapid progressive disease. Results from a long-term, randomised, comparative study of insulin or sulphonylurea treatment.

30. Authors - Fanghanel G. Sanchez-Reyes L. Trujillo C. Sotres D. Espinosa-Campos J.
Title - Metformin’s effects on glucose and lipid metabolism in patients with secondary failure to sulfonylureas.

31. Authors - Ravnik-Oblak M. Mrevlje F.
Title - Insulin versus a combination of insulin and sulfonylurea in the treatment of NIDDM patients with secondary oral failure.

32. Authors - Calle-Pascual AL. Garcia-Honduvilla J. Martin-Alvarez PJ. Vara E. Calle JR. Munguira ME. Maranes JP.
Title - Comparison between acarbose, metformin, and insulin treatment in type 2 diabetic patients with secondary failure to sulfonylurea treatment.
33. Authors - Ohkubo Y. Kishikawa H. Araki E. Miyata T. Isami S. Motoyoshi S. Kojima Y. Furuyoshi N. Shichiri M.

Title - Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study.
Source - Diabetes Research & Clinical Practice. 28(2):103-17, 1995 May.

34. Authors - Landstedt-Hallin L. Adamson U. Arner P. Bolinder J. Lins PE.

Title - Comparison of bedtime NPH or preprandial regular insulin combined with glibenclamide in secondary sulfonylurea failure.

35. Authors - Coniff RF. Shapiro JA. Seaton TB. Hoogwerf BJ. Hunt JA.

Title - A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes.

36. Authors - Chow CC. Tsang LW. Sorensen JP. Cockram CS.

Title - Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients.

37. Authors - Riddle M. Hart J. Bingham P. Garrison C. McDaniel P.

Title - Combined therapy for obese type 2 diabetes: supppertime mixed insulin with daytime sulfonylurea.

38. Authors - Klein W.
Title - Sulfonylurea-metformin-combination versus sulfonylurea-insulin-combination in secondary failures of sulfonylurea monotherapy. Results of a prospective randomized study in 50 patients.

39. Authors - Groop L. Widen E.
Title - Treatment strategies for secondary sulfonylurea failure. Should we start insulin or add metformin? Is there a place for intermittent insulin therapy?.

40. Authors - Paterson KR. Wilson M. Kesson CM. Buchan M. Roberts M. Reith SB. Davidson E.
Title - Comparison of basal and prandial insulin therapy in patients with secondary failure of sulphonylurea therapy.

41. Authors - Sotaniemi EA. Vierimaa E. Huupponen R. Karvonen I. Vuoti MJ. Rytomaa K.
Title - Insulin and sulphonylurea in the therapy of type 2 diabetes.

42. Authors - Groop L. Widen E. Franssila-Kallunki A. Ekstrand A. Saloranta C. Schalin C. Eriksson J.
Title - Different effects of insulin and oral antidiabetic agents on glucose and energy metabolism in type 2 (non-insulin-dependent) diabetes mellitus.

43. Authors - Lewitt MS. Yu VK. Rennie GC. Carter JN. Marel GM. Yue DK. Hooper MJ.
Title - Effects of combined insulin-sulfonylurea therapy in type II patients.[comment].
44. Authors - Casner PR.
Title - Insulin-glyburide combination therapy for non-insulin-dependent diabetes mellitus: a long-term double-blind, placebo-controlled trial.

45. Authors - Lins PE. Lundblad S. Persson-Trotzig E. Adamson U.
Title - Glibenclamide improves the response to insulin treatment in non-insulin-dependent diabetics with second failure to sulfonylurea therapy.

46. Authors - Holman RR. Steemson J. Turner RC.
Title - Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement.

47. Authors - Samanta A. Burden AC. Kinghorn HA.
Title - A comparative study of sulphonylurea and insulin therapy in non insulin dependent diabetics who had failed on diet therapy alone.

48. Authors - Quatraro A. Consoli G. Ceriello A. Giugliano D.
Title - Combined insulin and sulfonylurea therapy in non-insulin-dependent diabetics with secondary failure to oral drugs: a one year follow-up.

49. Authors - Mauerhoff T. Ketelslegers JM. Lambert AE.
Title - Effect of glibenclamide in insulin-treated diabetic patients with a residual insulin secretion.
50. Authors - Falko JM. Osei K.
Title - Combination insulin/glyburide therapy in type II diabetes mellitus. Effects on lipoprotein metabolism and glucoregulation.

51. Authors - Groop L. Harno K. Nikkila EA. Pelkonen R. Tolppanen EM.
Title - Transient effect of the combination of insulin and sulfonylurea (glibenclamide) on glycemic control in non-insulin dependent diabetics poorly controlled with insulin alone.

52. Authors - Groop L. Harno K. Tolppanen EM.
Title - The combination of insulin and sulphonylurea in the treatment of secondary drug failure in patients with type II diabetes.

53. Authors - Sargin H. Sargin M. Altuntas Y. Sengul AM. Orbay E. Seber S. Ucak S. Yayla A.
Title - Comparison of lunch and bedtime NPH insulin plus mealtime insulin Lispro therapy with premeal regular insulin plus bedtime NPH insulin therapy in type 2 diabetes.

54. Authors - Raskin P. Bode BW. Marks JB. Hirsch IB. Weinstein RL. McGill JB. Peterson GE. Mudaliar SR. Reinhardt RR.
Title - Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: A randomized, parallel-group, 24-week study.

55. Authors - Schwartz S. Sievers R. Strange P. Lyness WH. Hollander P.
Title - Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: Efficacy, safety, and cost analysis.
Title - Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients.

57. Authors - Hwu C-M. Ho L-T. Fuh MMT. Siu SC. Sutanegara D. Piliang S. Chan JCN.
Title - Acarbose improves glycemic control in insulin-treated Asian type 2 diabetic patients: Results from a multinational, placebo-controlled study.

58. Authors - Stehouwer MHA. DeVries JH. Lumeij JAE. Ader HJ. Engbers AMS. van Iperen A. Snoek FJ. Heine RJ.
Title - Combined bedtime insulin - Daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: Effects on HbA1c and hypoglycaemia rate - A randomised trial.

Title - Efficacy and safety of acarbose in insulin-treated patients with type 2 diabetes.

60. Authors - Robinson AC. Burke J. Robinson S. Johnston DG. Elkeles RS.
Title - The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control.

61. Authors - Riddle MC. Schneider J.
Title - Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone.

62. Authors - Feinglos MN. Thacker CR. Lobaugh B. DeAtkine DD. McNeill DB. English JS. Bursey DL.
Title - Combination insulin and sulfonylurea therapy in insulin-requiring type 2 diabetes mellitus.

63. Authors - Anderson JH Jr. et al
Title - Improved mealtime treatment of diabetes mellitus using an insulin analogue.

64. Authors - Saudek CD. Et al
Title - Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: A randomized clinical trial.

65. Authors - Clauson P. Karlander S. Steen L. Efendic S.
Title - Daytime glibenclamide and bedtime NPH insulin compared to intensive insulin treatment in secondary sulphonylurea failure: A 1-year follow-up.

66. Authors - Taylor R. Foster B. Kyne-Grzebalski D. Vanderpump M.
Title - Insulin regimens for the non-insulin dependent: Impact on diurnal metabolic state and quality of life.
67. Authors - Giugliano D. Quatraro A. Consoli G. Minei A. Ceriello A. De Rosa N. D'Onofrio F.
Title - Metformin for obese, insulin-treated diabetic patients: Improvement in glycaemic control and reduction of metabolic risk factors.

68. Authors - Riddle MC. Hart JS. Bouma DJ. Phillipson BE. Youker G.
Title - Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetic subjects.

69. Authors - Tindall H. Bodansky HJ. Stickland M. Wales JK.
Title - A strategy for selection of elderly Type 2 diabetic patients for insulin therapy, and a comparison of two insulin preparations.

70. Authors – Fritsche A. Schweitzer MA. Haring HU. 4001 Study Group.
Title - Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial.

71. Authors Roach P. Strack T. Arora V. Zhao Z.
Title - Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes.

72. Authors – Taylor R. Davies R. Fox C. Sampson M. Weaver JU. Wood L.
Title - Appropriate insulin regimes for type 2 diabetes: a multicenter randomized crossover study.
73. Authors – Bastyr EJ 3rd. Stuart CA. Brodows RG. Schwartz S. Graf CJ. Zagar A. Robetson KE.
Title - Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group.[comment].
Source - Diabetes Care. 23(9):1236-41, 2000 Sep.

Title - Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus.

75. Authors - Wolffenbuttel BH. Sels JP. Rondas-Colbers GJ. Menheere PP. Nieuwenhuijzen Kruseman AC.
Title - Comparison of different insulin regimens in elderly patients with NIDDM.


78. Authors - Anonymous.
Title - Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group

Title - Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group.
Source - Clinical Therapeutics. 21(3):523-34, 1999 Mar.

80. Authors – Roach P. Yue L. Arora V..
Title - Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 Study Group.

81. Authors – Riddle MC. Rosenstock J. Gerich J.
Title - The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients.
Source - Diabetes Care 26 (11): 3080-86, 2003 Nov

82. Author - Wright A, Burden AC, Paisey RB, Cull CA, and Holman RR, U.K. Prospective Diabetes Study Group
Title - Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57).

83. Author – Davies M, Storms F, Shutler S, Bianchi-Biscay M, and Gomis R. for the AT.LANTUS Study Group
Title – Improvement of Glycaemic Control in Subjects With Poorly Controlled Type 2 Diabetes
Title – Comparison of Basal Insulin Added to Oral Agents Versus Twice-Daily Premixed Insulin as Initial Insulin Therapy for Type 2 Diabetes
Source – Diabetes Care 28 (2): 254-59, 2005 Feb

Title – Initiating Insulin Therapy in type 2 Diabetes
Source – Diabetes Care 28 (2): 260-65; 2005, Feb

Title – Therapy after single oral agent failure: adding a second oral agent or an insulin mixture?

Title – Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin

88. Author – Christiansen J, Vaz J, Metelko Z, Bogoev M and Dedov I.
Title – Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemic, in patients with type 2 diabetes
Source – Diabetes, Obesity and Metabolism 5: 446-54; 2003