A Community Based Approach to Glucose Optimisation for Type 2 Diabetes

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A thesis submitted to the Faculty of Clinical Medicine at the University of Oxford for the degree of Doctor of Philosophy

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Preface

Throughout my medical training I have been drawn towards situations in which significant differences could be made to the lives of large numbers of people. This has led me to undertake clinical and research work in the fields of public health and primary care and in particular to be interested in improvements in healthcare delivery which could impact on the quality of life and outcome for entire disease populations.

I became interested in type 2 diabetes mellitus and its complications in my intercalated year as a medical student and encountered many individuals with this condition in my further clinical training. A growing interest led me to speak to Professor Robert Turner, director of UKPDS and international authority in diabetes care and I was thrilled to be invited to join his team in January 1999 with the remit of exploring the possible application of the gains in knowledge achieved in UKPDS to general practice. It was with enormous sorrow that I learnt of his untimely death in August 1999.

I was delighted to be able to continue this work with his colleague, Professor Rury Holman, with the same remit. The project would include an exploration of the potential difficulties in recruiting practices and patients to a programme of glucose optimisation as well as an actual study of glucose control and its effects, in order to lay firm proposals for the introduction of these ideas in practice. One problem of this approach was that a full outcome trial would take a large team many years to complete and was beyond the scope of this thesis. The objective therefore was to provide a broad exploration of the problems in this area in order to be able to proceed to international trials and application. I was pleased when the work was accepted by the University in 1999 and D Phil status confirmed in 2001.

In carrying out this study I have been surprised by the pandemic nature of the problem, the enormous health, social and economic burden and the level to which current clinical care falls short of its potential. This thesis suggests that improvements in care could be made with simple protocols and current therapies.

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Enormous gratitude is owed to the late Professor Robert Turner for his original research concept and enthusiasm for the implementation of UKPDS ideas in general practice.

I would like to thank my D Phil supervisors Professor David Mant and Professor Rury Holman for their ongoing support, involvement and critical appraisal of this work and to the staff of the Diabetes Trials Unit and Department of Primary Care for their assistance. Of particular note was the practical support provided by the research nurses Christina Dudley, Beryl Barrow and Katy Davidson, the deltagraph expertise of Dr Carole Cull and the advice on questionnaire selection given by Dr Andrew Farmer. I would like to express my thanks to the administrative, laboratory and information technology staff too for their continued help in facilitating this project.

I am indebted to the practice nurses, general practitioners, practice managers and receptionists within the clinical centres for undertaking this work and to all the patients involved in the project for their help, enthusiasm and continued feedback regarding the programme.

I would like to acknowledge financial support from the NHS R&D SE Training Fellowship scheme and Diabetes Trials unit and pharmaceutical assistance from GlaxoSmithkline for provision of Rosiglitazone, Medisense for provision of meters and Diabetes UK for provision of training and educational materials

Finally I owe a very special thanks to my husband Simon and my parents for their unstinting love, encouragement and support throughout this project.

Memorandum

The study, analysis and interpretation presented in this thesis are the original work of the author, carried out under the supervision of Professors David Mant and Rury Holman in the Department of General Practice, Institute of Health Sciences and Diabetes Trials Unit, Nuffield Department of Clinical Medicine at the University of Oxford. The processing of samples was done by the Diabetes Trials Unit Biochemistry Laboratory and Diabetes Research Laboratory at the University of Oxford.

I hereby declare that no part of this thesis has been submitted for any other degree at this or any other universities, although most parts of the work have been published in abstract form.

Abstract

A Community Based Approach to Glucose Optimisation for Type 2 Diabetes

Nicolette Potts, Green College, DPhil Thesis, Trinity Term 2003

Background: Attaining optimal glucose control in type 2 diabetes (T2DM) is essential to minimise complications, but difficult to achieve in practice with declining β-cell function in patients.

Aim: To evaluate the efficacy and feasibility of a protocol-led, treat-to-target approach emphasising earlier oral hypoglycaemic agent (OHA) combination and insulin use to target basal and prandial glucose in primary care.

Methods: T2DM patients aged 40-75 years, with glycosylated haemoglobin (HbA_{1C}) 6.4-10.0% on diet or oral monotherapy in 7 practices were asked to participate in a protocol-led, target-driven programme of care using early OHA and insulin therapy combinations to target basal and prandial glucose. Recruited patients were randomised to pre-specified algorithms with monthly therapy adjustment aiming for fasting plasma glucose values (FPG) <6mmol/L and 2-hour post-prandial (PPG) <8mmol/L. Isophane or humalog insulin was added where glucose targets were not attained. All patients were reviewed at one year. Glucose, weight and cardiovascular (CVS) risk factor outcomes were measured and the feasibility, acceptability and safety of the programme evaluated with validated questionnaires.

Results: 345 patients were studied. 60 participated in the glucose study and 285 received standard care. 65% of recruited patients were male, with mean (SD) age 61.0 (8.2) years, BMI 29.8 (5.3) kg/m^2, HbA_{1C} 7.5 (0.9)% and median (IQR) T2DM duration 3 (1-5) years. 41 completed the study. Glucose control was significantly improved in recruited compared to non-recruited patients with a mean overall 0.8% HbA_{1c} reduction and 72% patients achieving HbA_{1c}<7% and 64% <6.5% at 1 year. Therapy use was also significantly increased with 50% requiring 3 therapies, 30% 2 and 10% monotherapy. 24 (59%) of recruited patients received isophane and 16 (39%) humalog to achieve targets. Glucose optimisation was achieved without significant hypoglycaemia or adverse events and patient quality of life (QoL) and therapy satisfaction remained high. CVS risk was reduced in recruited patients.

Conclusions: A more structured, target-driven approach to glucose optimisation can successfully achieve normoglycaemia in a selected primary care T2DM population without significant adverse events, hypoglycaemia. or QoL impairment in patients. A principal barrier to wider implementation of this programme appears to be practice and patient participation.

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Glossary

AACE	American Association of Clinical Endocrinologists
ABCD	Appropriate Blood Pressure Control in Diabetes
ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
ADS	Appraisal of Diabetes Scale
ALLHAT	Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
ASCOT	Anglo-Scandinavian Cardiac Outcome Trial
ATP	Adenosine triphosphate
AUC	Area under the curve
BARI	Bypass Angioplasty Revascularisation Initiative
BHS	British Hypertension Society
BMI	Body Mass Index
BP	Blood pressure
C3	Complement factor C3
CAD	Coronary Artery Disease
CAPPP	Captopril Prevention Project
CARE	Cholesterol and Recurrent Events Trial
CCAIT	Canadian Coronary Atherosclerosis Intervention Trial
CCB	Calcium Channel Blockers
CCF	Congestive Cardiac Failure
CHD	Coronary Heart Disease
CI	Confidence interval
CIT	Conventional insulin injection therapy
CODE-2	Costs of Type 2 Diabetes in Europe Study
CRF	Case Report Form
CRP	C reactive protein
CSII	Continuous subcutaneous insulin infusion
CV	Coefficient of Variation
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease

CVS	Cardiovascular
DAIS	Diabetes Atherosclerosis Intervention Study
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DECODE	Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe
DFR	Data file repository
DIS	Diabetes intervention study
DNA	Deoxyribonucleic acid
DPP	Diabetes prevention project
DPS	Diabetes prevention study
DRL	Diabetes research laboratories
DRS	Digital retinal screening
DSN	Diabetes specialist nurse
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTU	Diabetes Trials Unit
DUK	Diabetes United Kingdom
DVLA	Driving Vehicle Licensing Authority
EBM	Evidence based medicine
ECG	Electrocardiogram
EDPG	Early diabetes prevention group
EQ-5D	EuroQoL 5 dimensions questionnaire
EQ-5VAS	EuroQoL visual analogue scale for overall health
ETDRS	Early Treatment of Diabetic Retinopathy Study
EtOH	Alcohol
FACET	Fosinopril Amlodipine Cardiovascular Events Trial
FBC	Full blood count
FP10	The form used to issue a prescription to an NHS patient by a GP
FPG	Fasting plasma glucose
GCP	Good clinical practice
GFR	Glomerular filtration rate
GISSI	Gruppo Italiano per lo Studio della Soprarvivenza nell'Infarto Miocardio trials
GMS	General Medical Services
GP	General practitioner
GOOD	Glycaemic optimisation outcomes in diabetes
Hb	Haemoglobin
HbA_{1c}	Glycosylated haemoglobin

HBGM	Home blood glucose monitoring
HDFP	Hypertension Detection and Follow Up Program
HDL	High density lipoprotein
HHS	Helsinki Heart Study
HIP	Health improvement priority
HLA	Human leucocyte antigen
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension optimal treatment study
IAUC	Incremental area under the curve analysis
ICH	International conference on harmonisation
IFG	Impaired fasting glucose
IGF	Insulin growth factor
IgG	Immunoglobulin G
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
IQR	Interquartile range
IRAS	Insulin resistance atherosclerosis study
ITT	Intention to treat data analyses
JHG	Joint heart guidelines
JNC VI	Joint National Committee VI
LDL	Low density lipoprotein
LIPID	Long term intervention with pravastatin in ischaemic heart disease study
Lp(a)	Lipoprotein a
Mg	Milligrams
MI	Myocardial infarction
MIT	Multiple insulin injection therapy
Mmol	Millimole
NDM	Non diabetes mellitus
NEFA	Non esterified fatty acids
NGT	Normal glucose tolerance
NHANES	National Health and Nutrition Examination Surveys
NHS	National health service (UK)
NHS R&D	National Health service research and development
NICE	National Institute of Clinical Excellence
NIDDM	Non insulin dependent diabetes mellitus
NIH	National Institutes of Health

NORDIL	Nordic Diltiazem Study
NSF	National Service Framework
OCDEM	Oxford Centre for Diabetes, Endocrinology and Metabolism
OGTT	Oral glucose tolerance test
OHA	Oral hypoglycaemic agent
OR	Odds ratio
PAD	Peripheral arterial disease
PAI-1	Plasminogen activator inhibitor – 1
PCG	Primary care group
PCT	Primary care trust
PPARγ	Peroxisome proliferator activated receptor gamma
PPG	Post prandial glucose
PVD	Peripheral vascular disease
QoL	Quality of life
R&D	Research and Development
RCP	Royal College of Physicians
RCT	Randomised controlled trial
SBGM	Self blood glucose monitoring
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDIS	Stockholm Diabetes Intervention Study
SENDCAPS	St Mary's Ealing Northwick Park Diabetes CVD Prevention Study
SHEP	Systolic Hypertension in the Elderly Program
STOP-2	Swedish Trial in Old Patients with Hypertension
SU	Sulphonylurea
SYST-EUR	Systolic Hypertension in Europe Trial
SYST-CHINA	Systolic Hypertension in China
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
tPA	Tissue plasminogen activator
TZD	Thiazolidinedione
UGDP	University Group Diabetes Programme
UKPDS	United Kingdom Prospective Diabetes Study
VACSDM	Veterans Affairs Cooperative Study on Glycaemic Control and Complications

VC	Valid case
VLDL	Very low density lipoprotein
WBQ-12	Well-being questionnaire 12 item version
WHO	World Health Organisation
XS	Cross-sectional

Chapter 1: Introduction

Type two diabetes mellitus (T2DM) is a substantial global health concern of epidemic proportions. Worldwide prevalence is soaring and morbidity and mortality are extensive. Diabetes management poses a huge social and economic burden accounting for 10% of total NHS resources. The major impact of this chronic disorder lies in its complications. T2DM is the fourth leading cause of death with a 2-fold excess mortality, 2-4 fold increased risk of CHD and stroke, 3-5 fold higher cerebral vascular mortality and 4-6 fold increased peripheral arterial disease risk. Retinopathy affects 44% of patients, nephropathy 25% and neuropathy 42%.

The importance of glucose control in reducing complications in T2DM patients is well recognised. The Kumamoto and UKPDS results confirm that improved glycaemic control reduces the risk of diabetic complications, that there is no HbA1c "threshold" for increased risk and that T2DM is a disorder characterised by progressively declining β-cell function and increasing hyperglycaemia with time. Elevated glucose levels are the principal predictor of microvascular complications and an important modifiable risk factor for macrovascular disease in T2DM.

The healthcare burden of T2DM is increasingly shifting from a secondary to primary care setting yet standards of care remain patchy with considerable variation in quality and service delivery. The optimal model of T2DM care in general practice has not been defined but unstructured care has been associated with worse glycaemic control and greater mortality than secondary care.

The challenge is to determine how best to attain and maintain normoglycaemia in a routine general practice setting with implementation of structured intensive management policies to minimise morbidity and mortality whilst safeguarding patient quality of life. The feasibility, acceptability and safety of policies must be determined and their efficacy on glucose lowering and cardiovascular risk modification assessed.

This study was conducted with these objectives in mind. A protocol-driven, treat-to-target approach for glucose control with earlier use of OHA combinations and insulin was designed and its efficacy, safety and acceptability tested in general practices over one year. The feasibility of attaining fasting and prandial normoglycaemia was determined and biochemical, clinical and psychological consequences for patients explored. The number of therapies required, adherence, acceptability and safety of earlier use of OHA combinations and insulin in primary care was tested and the willingness of patients and practices to participate gauged. Finally the magnitude of the potential

benefits of the programme was estimated by comparing outcomes for the cohort of recruited patients with those who continued to receive standard general practice care over the same time period.

An important outcome of the work undertaken is that it informs the design of a definitive clinical trial of glucose optimisation and cardiovascular disease in primary care T2DM, and assists future formulation of therapeutic strategies to enhance T2DM management in primary care. Cost analyses are underway which will be used to assist generalised application of these findings to practices and to inform local and national health policy decisions, but these do not form part of this thesis.

This thesis is divided into 4 sections. The first section describes the background literature, rationale and objectives of the study. An epidemiological overview of diabetes and its complications is provided in chapter 2 whilst chapter 3 provides a comprehensive review of the literature relating to glucose control, microvascular and macrovascular complications. Research evidence concerning the delivery of T2DM care in general practice is summarised in chapter 4 and the section concludes with a description of the rationale and objectives for this D Phil thesis.

The second section of the thesis describes the study methodology with particular emphasis on the design, population, interventions and outcomes involved. Information regarding ethical approval, funding, indemnity and data handling is summarised at the end of chapter 5.

Section three summarises the results of the study. The feasibility of this approach in general practice is examined in chapter 6 with respect to participation of practices and patients, safety, acceptability and adverse events. The efficacy of the programme is evaluated in chapter 7 in terms of glucose control, weight change, hypoglycaemia episodes and cardiovascular (CVS) risk factor modification and the potential achievable benefits of glucose optimisation compared with standard care are estimated. Therapy algorithms applied for potential use in a large-scale trial are discussed and their comparative efficacy gauged in chapter 8.

Finally results are discussed and conclusions made in chapters 9 and 10, within section four.

Section One: Background and Aims

Chapter 2: Diabetes Mellitus

2.1: Definition

Diabetes mellitus is a heterogeneous syndrome with interrelated metabolic, vascular and neuropathic components. Abnormal carbohydrate, fat and protein metabolism arise from diminished insulin secretion and/or ineffective insulin action. Hyperglycaemia is a central metabolic parameter used for diagnostic and therapeutic evaluation. Macroangiopathy, microangiopathy, peripheral and autonomic neuropathy are common complications.

2.2: Diagnosis and Classification

Diabetes diagnosis is confirmed by two random venous plasma glucose concentrations of >11.0 mmol/L or fasting venous plasma glucose concentrations >7.0 mmol/L. Four classes are recognised: type 1 diabetes (T1DM) with β-cell destruction and absolute insulin deficiency (ketosis-prone); type 2 diabetes (T2DM) characterised by insulin resistance and relative insulin deficiency (ketosis-resistant); other specific types secondary to genetic, pancreatic, endocrine disease, infections and drugs; and gestational diabetes where initial onset or recognition of diabetes or IGT occurs in pregnancy. Two categories of glucose homeostasis: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are defined using an oral glucose tolerance test (OGTT). IGT is characterised by a 2-hour level of > 7.0 mmol/L but < 11.1 mmol/L and IFG by a fasting value of > 6.1mmol but < 7.0 mmol/L.

T2DM constitutes 90% of all cases of diabetes mellitus (Dagogo, 1997) and occurs predominantly in people over forty years. The peak prevalence in Western countries is 70-80 years. Onset is insidious, preceding clinical diagnosis by 4-7 years (Harris, 1993). The rate of diagnosis for T2DM is 0.3-2.0 per 1000 person years. 84.3% of patients are diagnosed in general practice; 53% from diabetes symptoms, 16% from infections, 1.7% from complications and 29% from incidental glycosuria. One-third to one half of all diabetes cases are undiagnosed (Alberti, 1988).

2.3: Epidemiology of Diabetes

Diabetes mellitus is now a substantial global health concern of epidemic proportions. Currently affecting 4.8% of Europid, 14.6% of Afrocarribean, 19.6% of Asian populations (McKeigue, 1992) and 10-20% of elderly subgroups, worldwide prevalence is expected to increase from 130 million in

1997 to 300 million in 2025 (King, 1993; King, 1998). The major part of this numerical increase will occur in developing countries (170%) and by the year 2025, more than 75% of people with diabetes will reside in the developing world.

Within the UK, diabetes mellitus affects 1.4 million people, 60,000 new cases are reported annually, and a diabetic population of 3 million is expected by 2010. An equal number of people will remain undiagnosed (Harris, 1993). Rising obesity and an ageing population are the principal causes for this doubling in prevalence but recent WHO changes in diagnostic criteria lowering the threshold for defining diabetes also result in increased reported prevalence.

The social and economic burden of diabetes management is enormous. Diabetes currently accounts for 15% ($100 billion) USA health expenditure (Rubin, 1992) and 10% (£2 billion/year) NHS costs (Audit Commission,2000). Hospital costs are six times higher for diabetic than non-diabetic patients and hospital bed occupancy for diabetic patients (6-16%) is double that of other patient categories combined. In 1996 diabetic patients accounted for 5.4% of hospital episodes, 6.4% of outpatient attendances and 9.4% of UK inpatient bed days. T2DM complications increase NHS costs more than five-fold and increases by five the chance of a person needing hospital admission. Significant direct personal costs are also incurred (£802/year plus loss of earnings).

The major impact of diabetes resides in its complications. T2DM is the fourth leading cause of death in developed countries with a 2-fold excess mortality (UKPDS 23, 1998), a 2-4 fold increased risk of CHD and stroke, 3-5 fold higher cerebral vascular mortality and 4-6-fold increased peripheral arterial disease (PAD) risk (Kannel 1979, Krowelski 1977, Kessler 1971, Fuller 1983, Panzram 1987, Ford 1991, Abbott 1987, Barrett-Connor 1988, Sasaki 1989, Manson 1991 Wilson 1991, Koskinen 1992 Stamler 1993, Biller 1993, Laakso 1997, UKPDS 29 1999). 30% of T2DM develop clinical complications within ten years of diagnosis (UKPDS 16, 1995) and 70% of US diabetes-related hospitalisations (Geiss, 1995) and 59% deaths are from CVD. Each year in the UK 20,000 premature deaths occur in diabetic patients and age-adjusted life expectancy is decreased on average by 5-10 years (Panzram, 1987).

Morbidity associated with diabetes is also substantial. Ten year incidence of blindness and retinopathy in diabetic patients is 18% and 67% (Klein, 1995). Diabetic patients are 23 times more likely to become blind, 50 times more likely to develop foot ulcers and 27 times more likely to require lower limb amputation than their non-diabetic contemporaries. In addition, 40% have nephropathy, 42% peripheral neuropathy and 55% of male diabetics over sixty years are impotent.

Psychological morbidity, due to decreased mobility, sleep, energy, mood and social interaction, is also highly significant.

2.4: Complications

Complications are the principal factor governing quality of life and medical outcome in T2DM patients. Key components include macroangiopathy (coronary artery disease, peripheral vascular disease and cerebrovascular disease), microangiopathy (retinopathy, nephropathy) and neuropathy (peripheral and autonomic neuropathy).

50% of newly diagnosed T2DM patients have diabetic tissue damage (UKPDS 8, 1991) and within 15 years of diagnosis, 28% of T2DM patients have died from a diabetes related cause, 23% have had a significant microvascular complication (usually laser photocoagulation) or cataract extraction, 27% have sustained an MI and 10% a CVA. Macrovascular disease is the leading cause of morbidity and death accounting for 75% of deaths (Bierman, 1992). The prevalence of complications in a recent Netherlands study were CHD 48%, hypertension 56%, CVA 15% PAD 35% with 80% reporting neuropathy symptoms (Ross, 1993).

2.4.1: Macrovascular Complications

Epidemiology of macrovascular disease in T2DM

Hypertension prevalence is doubled in T2DM (Klein 1995, Teuscher 1988) with 25% patients affected at diagnosis and 50% eventually needing treatment. Associated morbidity and mortality is substantial. Hypertension was associated with a 2-4 fold increased mortality in the London cohort of the WHO study of Vascular Disease in Diabetes and a sharp increase in 10-year CHD mortality was seen in diabetic persons with SBP>152mmHg in the Whitehall Study. Similarly the Schwabing Study reported a strong correlation between SBP and DBP and subsequent CVD in diabetes. (Wolffenbuttel, 1993).

Coronary, cerebral and peripheral vessel atherosclerosis is increased in T2DM and a 2-fold excess cardiovascular and cerebrovascular mortality is reported (Jarrett 1982, Stengard 1992). CVS complications are 2-6 times greater than microvascular complications and over 60% of diabetes deaths are due to CVD (Geiss 1995, Schernthaner 1996). Age-adjusted incidence of fatal CHD in T2DM patients is 1-4% (Pan 1986, Stamler 1993, Kannel 1979) and prognosis after both MI and CVA are significantly reduced (Zuanetti, 1993). 5 year mortality rates post-MI of 72% in diabetics

and 50% in non-diabetics are reported and both disability and recurrence rates are increased (Gray 1989, Olsson 1990). Lipid abnormalities, comprising elevated LDL and VLDL, and reduced HDL-cholesterol levels are seen in 40-50% T2DM patients.

2.4.2: Microvascular Complications

Retinopathy

Diabetic retinopathy affects 15-25% of T2DM patients at diagnosis (Klein,1984) and 12-44% at 10 years, and is the commonest cause of blindness under 65 years (19.7% cases). Retinopathy incidence is closely related to T2DM duration and glycaemic control; 20% and 80% of patients have retinopathy after ten and twenty years respectively and incidence rates of 60/1000 (all retinopathy) and 8/1000 (proliferative) person years are reported locally.

Estimated annual incidence rates of blindness in the general population attributable to diabetes are 1.6-2.1 per 100 000 and five year rates of legal blindness are 2% in T2DM patients. Retinopathy is now the leading cause of visual disability in middle aged populations within advanced societies and visual loss is 25 times commoner in diabetics than non-diabetics. Comprehensive screening and treatment for diabetic retinopathy prevents 260 new cases of blindness every year in the UK.

Cataract is the commonest T2DM ocular complication with a prevalence of 60% in the age group 30-54 years. Oculomotor, trochlear or abducens mononeuropathies, corneal abrasions, open angle glaucoma, rubeosis iridis, myopia, pupillary and accommodation abnormalities are also increased.

Distinct stages of retinopathy development are characterised. Hyperglycaemia in T2DM initially causes basement membrane thickening, pericyte loss and hyperperfusion of the retinal circulation. Retinal vein dilatation characterises the stage of preretinopathy. Classic background retinopathy changes including intramural capillary pericyte loss, capillary non-perfusion, microaneurysm formation, excess vascular permeability, hard exudates, haemorrhages and retinal oedema generally appear within two years. A preproliferative stage is recognised with terminal arteriole occlusion (cotton wool spots), segmental venous dilatation (beading), haemorrhages and intraretinal microvascular abnormalities. Finally angiogenesis factors from ischaemic retinal tissues promote a proliferative retinopathy stage with the characteristic appearances of neovascularisation, fibrosis, retinal detachment, vitreous haemorrhage, neovascular glaucoma in 5-10% of patients. Visual loss results from these or macular oedema. The role of hormonal and genetic risk factors in the aetiology of retinopathy remain controversial (Aiello 1993).

The principal treatment modalities for diabetic retinopathy are laser photocoagulation and vitrectomy. Photocoagulation causes regression of new vessels and reduces macular oedema; visual loss from severe proliferative retinopathy is reduced by >50% with panretinal therapy (DRS, 1978). Vitrectomy improves vitreous haemorrhage and retinal detachment of the central macula. Prompt treatment of fibrovascular proliferation, extensive preretinal haemorrhage and traction of the disc, macula and peripapillary retina have recently proved beneficial (DRVSRG, 1985).

Nephropathy

The cumulative incidence of microalbuminuria and clinical nephropathy in European T2DM patients is 20-25%. Diabetes causes end stage renal failure in 17% of dialysis patients (Geerlings, 1994) and all-cause mortality ratios for patients with heavy proteinuria are 2.8 after a mean 9.4 years (WHO, 1985). Hyperfiltration, increased intraglomerular pressure, renal hypertrophy, progressive albuminuria, rising systemic blood pressure, declining glomerular filtration rate (GFR) and end stage renal failure characterize nephropathy development. Urinary albumin concentration doubles within six years in normoalbuminuric type two patients, the annual rate of increase being 16.4% (UKPDS 9 1993, Schmitz 1988).

Hyperglycaemia exacerbates nephropathy development through collagen glycation (increasing basement membrane permeability, glomerular filtration rate and glomerular hyperfiltration), polyol pathway activation, protein kinase C activation and increased growth factor production. Genetic and renal structural factors (reduced size and number of glomeruli in low birth weight infants), high protein intake and free radical glomerular injury are contributory. (Wiseman, 1984, Remuzzi 1994)

Systolic blood pressure (SBP) and average albumin excretion determine nephropathy progression. Approximately 25% of T2DM patients develop microalbuminuria within six years and 32% of these progress to clinical nephropathy in four years (Schmitz, 1988). Excess mortality is associated with increased CVS risk factors (hypertension, dyslipidaemia, smoking), insulin resistance, hyper-coagulability (hyperfibrinogenaemia, platelet aggregability, increased VIIc), excess microvascular or macrovascular disease in albuminuric patients (Haffner 1999,Gall 1995). 60% of T2DM patients with nephropathy die of renal failure.

Treatment strategies include intensive management of hypertension, dyslipidaemia and hyperglycaemia, ACE inhibition (reduces intraglomerular pressure) and dietary protein restriction, with haemodialysis, CAPD or renal transplantation reserved for end stage renal failure. The benefits of glycaemic control are lessened once macroalbuminuria is established.

Neuropathy

Peripheral neuropathy affects 41.6% of T2DM patients (Kumar, 1994) and 15.2% at diagnosis (Lehtinen, 1989). Chronic sensory polyneuropathies, acute painful neuropathy, proximal or diffuse motor neuropathies, focal vascular or pressure mononeuropathies and insulin neuritis may occur. Sorbitol accumulation and hyperglycaemia produce structural nerve damage and impaired conduction velocity by competitive inhibition of sodium-dependent myoinositol uptake and reduced Na-K-ATPase activity. Nerve fibre loss, segmental demyelination, axon regeneration/remyelination and endoneurial vascular abnormalities may occur. Deficient axonal transport, nerve protein glycation and reduced nerve growth factor are reported but the precise mechanisms underlying diabetic neuropathy are unclear. Sensory symptoms, reduced sensation, reflexes, muscle strength and abnormalities on electrophysiological, proprioception, vibration or thermal tests are detectable.

Treatments include control of hyperglycaemia, analgesics, tricyclics, tranquillizers, anticonvulsants, topical capsaicin or opsite for relief of neuropathic pain and physiotherapy for muscle wasting. New approaches including aldose reductase inhibitors, gangliosides (Horowitz, 1986), gamma-linolenic acid (Jamal, 1986) and lignocaine derivatives are currently being explored.

Autonomic dysfunction affects approximately 40% of people with T2DM. Postural hypotension, tachycardia, neuropathic oedema, gustatory sweating, respiratory arrest, diabetic diarrhoea, gastroparesis, neurogenic bladder and impotence are common clinical syndromes. Abnormal peripheral blood flow, oesophageal motility, gallbladder emptying and neuroendocrine responses are also characteristic.

2.4.3: Miscellaneous complications

Disorders of connective tissue (hyperostosis, osteoarthritis, osteolysis, scleroderma diabeticorum, carpal tunnel syndrome, Dupuytrens contracture, flexor tenosynovitis, adhesive capsulitis and shoulder hand syndrome), dermatopathies (necrobiosis lipoidica diabeticorum, vitiligo, granuloma annulare, bullosa diabeticorum) and infections are also increased in T2DM patients.

2.5: Management Strategies

2.5.1: Management Principles

The overriding goals of T2DM management are firstly to relieve symptoms and secondly to prevent the acute and chronic complications of the disease (Alberti, 1988). Whilst the former is generally achievable with maintenance of blood glucose levels below the renal threshold, the latter is more difficult, requiring long term attention to principles of self-care, healthy living, CVS risk factor modification, smoking cessation, glucose monitoring and intensive glucose control. Strategies for glucose control are discussed in detail in chapter 3. The section below summarises the evidence relating to multifactorial risk intervention.

2.5.2: The importance of multifactorial risk intervention

Insulin resistance and its associated features, dyslipidaemia, hypertension, alterations in fibrinolysis and platelet function precede and predict T2DM. Consequently when the diagnosis of T2DM is made based on blood glucose measures, multiple cardiovascular risk factors have already been present for years. Merely lowering glucose does not therefore abolish the increased risk of CVD in T2DM patients. Data from recent intervention trials confirm that macrovascular disease prevention depends on effective hypertension and hyperlipidaemia management in addition to hyperglycaemia control.

Prevention of dyslipidaemia

The prevalence of dyslipidaemia in T2DM patients is high. The mean LDL-cholesterol in 594 T2DM patients in IRAS (Haffner, 1999) was 3.6 mmol/L in insulin-resistant and 3.7 mmol/L in insulin-sensitive subjects Application of lipid guidelines recommending lipid-lowering therapy at LDL-cholesterol levels greater than 3.4 mmol/L, implies that >50% of T2DM patients may require treatment.

Primary and secondary prevention studies have revealed clear benefits of lipid management in T2DM. Primary prevention trials, including HHS (Frick, 1987), SENDCAP (Elkeles, 1998) and AFCAPS (Downs, 1998) demonstrated crude risk reductions of 68%, 68% and 21% in CVD with gemfibrozil, bezafibrate and lovastatin respectively whilst LDL-cholesterol reductions of 28%, 36% and 25% in the CARE (Goldberg, 1998), 4S (Pyorala, 1997) and LIPID (Lipid Study Group, 1998) secondary prevention statin trials were associated with a reduction in CVD events in T2DM patients

of 25%, 55% and 19% respectively. VA-HIT demonstrated a 6% increase in HDL-cholesterol and 24% reduction in MI/CHD death with gemfibrozil and DAIS confirmed benefits of fenofibrate with a 35% reduction in triglyceride and 23% reduction in clinical events. CCAIT, the Post Coronary Artery Bypass Graft Trial and HATS have reaffirmed these findings using angiographic end-points.(Yki Jarvinen 2000, Wild 1999).

The results of larger scale primary prevention hyperlipidaemia studies in T2DM including FIELD and CARDS are expected in 2004.

Prevention of hypertension

T2DM incidence is increased 2.5 times in hypertensive individuals and hypertension frequently arises in the pre-diabetic state associated with insulin resistance. This co-existence of pathologies leads to higher prevalence and CVS risk. The prevalence of hypertension in UKPDS T2DM patients was 39% (SBP>160/DBP>90) and application of the newer JNCVI guidelines (treatment for T2DM patients with SBP>130mmHg and DBP>85mmHg) suggests that over 50% of patients may require antihypertensive therapy.

Many randomised controlled trials have evaluated effects of antihypertensive therapy on CVS outcomes in T2DM. Only two, HDFP and SHEP (Curb, 1996), predated the UKPDS, reporting absolute risk reductions of 16.3 and 15.0/10^3 pyr for total CVD outcomes with stepped care and diuretic-based regimes. UKPDS (UKPDS 39, 1998) demonstrated a 44% CVA risk reduction, 32% CVS mortality risk reduction and 34% reduction in the deterioration of retinopathy with systolic and diastolic blood pressure reductions of 10mmHg and 5mmHg respectively. In the tight blood pressure group 29% patients required three or more therapies. The Syst-Eur and Syst-China (Tuomilehto, 1999) trials compared calcium channel blocker and placebo in subgroup diabetic participants demonstrating reductions in all-cause mortality of 55%, CVA 73% and all CVS events 69% with nitrendipine. Antihypertensives for isolated systolic hypertension in T2DM patients eliminated the excess CVS risk related to diabetes in this study. In the HOT (Hansson, 1998) trial the hypertensive diabetic subgroup of 1501 patients had a 50% lower risk of major CVS events with DBP <80 compared to <90mmHg. The HOPE (2000) study demonstrated clear benefits of ramipril therapy versus placebo but the MICRO-HOPE diabetic subgroup analyses did not have sufficient power to determine treatment effects.

Finally several studies have compared hypertension therapies in T2DM patients. The UKPDS suggested equal efficacy of captopril and atenolol in CVA prevention but the power of the study

was not sufficient to demonstrate differences between drugs. In contrast the CAPPP (Hansson 1998) study of 575 patients with hypertension and diabetes, suggested ACE superiority in reducing CVS events with a 66% lower rate of total and non-total MI with captopril compared with other conventional antihypertensive agents. Captopril use was also associated with a 22% reduction in the risk of developing diabetes in non-diabetics. The latter data were confirmed in the HOPE study. In this trial ramipril or placebo was administered to high-risk patients with a history of CAD, CVA, PVD or diabetes and at least one additional risk factor. A total of 3577 patients with diabetes (1135 with no clinical manifestation of CVD) were included in the study. Treatment with ramipril for 4 years significantly reduced rates of death from cardiovascular causes, MI, stroke, death from any case, revascularisation procedures, incidence of new diabetes (by 34%) and complications related to diabetes (by 16%) in the entire study group. The mean reduction in BP was small (3/2mmHg) and was estimated to maximally explain only 40% of the reduction in the rate of stroke and 25% of the reduction in the rate of MI. ACE inhibitors thus appeared to have beneficial effects on the heart and vasculature not attributed to their BP lowering actions. The ABCD (Estacio, 1998) trial reported a higher incidence of fatal and non-fatal MI with nisoldipine compared to enalapril (RR 9.5 95% CI:2.3-21.4) and the FACET (Tatti, 1998) trial in 380 hypertensive T2DM patients demonstrated a significantly lower risk of the combined outcome of acute MI, CVA or hospitalised angina with fosinopril versus amlodipine. The NORDIL (Hansson, 2000) subgroup trial of 721 diabetic participants and STOP-2 (Hansson, 1999) studies add to the controversy revealing similar efficacy of newer antihypertensive (CCB, ACE) and conventional therapies. Most recently the ALLHAT and ASCOT (2000) trials confirm these results.

Chapter 3: Glucose Control

3.1: Glucose control and complications

An association between hyperglycaemia and diabetes complications was first postulated in the early part of the last century but conclusive research evidence to confirm this association has really only emerged in the last three decades. This chapter provides a review of the evidence relating to glucose and T2DM complications, examines current therapeutic strategies and defines the need for a new T2DM treatment paradigm in primary care.

3.2: Glucose control and microvascular disease

3.2.1: Early animal and transplantation studies

Detailed animal experimental and transplantation studies by Lee (1974), Mauer (1975) and Miller (1976) provided early evidence of a correlation between glucose control and microvascular disease. IgG and C3 immunofluorescent staining after four to six months of hyperglycaemia in rats, disappeared within two months of renal transplantation from diabetic to normal rats and reappeared within two months of transplantation from normal to diabetic rats. Similar results were obtained in human transplantation studies (Abouna 1983, Mauer 1976, Bilious 1987).

Mauer demonstrated significantly greater staining of Bowmans capsule, tubule and glomerular basement membrane, and increased arteriolar hyalinosis in renal tissue from 12 diabetic compared to 17 non-diabetic patients 2-12 years after transplantation and complete resolution of diabetic renal abnormalities (increased mesangial matrix, glomerulosclerosis, capillary basement membrane thickening) was demonstrated within 7 months of renal transplantation to normal patients in studies by Abouna.

Finally, Engerman and Kern, investigating the effect of glucose control on retinopathy in normal and alloxan-induced diabetic dogs demonstrated inhibition of retinopathy development with good glycaemic control. This effect was markedly abated if glucose control was postponed many months after diabetes onset (Engerman, 1987).

3.2.2: Human cross-sectional, retrospective and clinical trial studies

Human cross-sectional, retrospective and clinical trial study data then followed. Pirart demonstrated a beneficial relationship between glucose control and retinopathy development in 4398 diabetic patients followed for 25 years from 1947 to 1973. 40% of patients with good glycaemic control in this study developed retinopathy compared with 80% of those with poor control and severe retinopathy was demonstrated in 15% of the latter group. Johnsson in a retrospective review of records for diabetic patients diagnosed between 1922 and 1945 revealed that treatment with multiple daily insulin injections and strict diet produced significantly less retinopathy than a single long-acting insulin regimen and less regimented diet (3% vs 19%). Similarly severe retinopathy was 2.5 times greater in type 1 patients with poor glycaemic control (mean HbA_{1c}>12.3%) than with good control (HbA_{1c}<10.9%) in a longitudinal study of 230 T1DM patients by Chase. Indeed, no subjects with HbA_{1c} <9.0% were found to have retinopathy. Age and diabetes duration were significant covariates in retinopathy development in this study. This finding was confirmed in the WESDR studies by Klein (1995) in a probability sample of 2990 patients selected from 10,135 diabetic patients receiving primary care in an 11 county area of S.Wisconsin where glycosylated haemoglobin was revealed as a significant independent predictor of incidence and progression of retinopathy adjusting for diabetes duration, age, sex and severity of retinopathy at baseline. The exponential relationship between worsening glycaemic control and incidence of complications was seen in both type 1 and 2 patients and was consistent for hyperglycaemia at any level.

Over 30 epidemiological studies examining the relationship between glucose and microvascular disease have been reported. Population-based, prevalence studies in T1DM initially demonstrated increased frequency of complications with duration of disease (Oakley 1974, Paz 1975, Kussman 1976, Palmberg 1981, Klein 1984-1988, Krolewski 1985-1987, Anderson 1983, Kofoed 1987). 20 epidemiological studies subsequently identified a strong independent association between glucose control and rate of microvascular complications in T2DM controlling for blood pressure, weight, insulin levels and disease duration; thirteen related to retinopathy development (Lee 1992, Hamman 1989, Howard-Williams 1984, Klein 1994, Stolk 1995, Nathan 1986, Morisaki 1994, Chen 1995, Liu 1993, Teuscher 1988, Haffner 1988, Ballard 1986, Knuiman 1986), five to nephropathy (Klein 1993, Wirta 1996, Ballard 1988, Fabre 1982, Humphrey 1989), and two to neuropathy (Partanen 1995, Lehtinen 1989). Early reviews concluded that the preliminary studies were sufficiently robust to establish a clear relationship between glucose control and diabetic microvascular complications (Cahill 1976, Tchobroutsky 1978 Brownlee 1979, Skyler 1979) and subsequent reviews followed (Skyler 1996, Edelman 1998, Hirsch 1998, Gaster 1998, Groeneveld 1999 Duckworth 2001).

3.2.3: Prospective randomised studies

Retinopathy

Prospective clinical trial data was initially less conclusive. The first prospective randomised study of glycaemic control, initiated at the Hotel Dieu in Paris, reported that attempts at careful blood glucose control resulted in slower progression of diabetic retinopathy (Eschwege 1979). The Steno group (Lauritzen, 1983 1985) evaluated 30 type 1 patients with background retinopathy randomly assigned to insulin therapy or CSII and the Kroc group (1984) performed a randomised pilot trial of 8 months duration in which 68 subjects from 6 UK and US centres were followed for 2 years. Finally the Oslo study (Dahl-Jorgensen 1986, Brinchmann-Hansen 1988) incuded 45 type 1 subjects randomised to conventional twice daily insulin, multiple insulin injections or CSII and 30 subjects with T1DM and microalbuminuria, and the Stockholm Diabetes Intervention (Reichard 1988-1993) Study randomised 102 T1DM subjects to standard insulin or improved metabolic control using intensified insulin treatment with evaluations at baseline, 18 months, 3, 5 and 7.5 years.

Despite improved glycaemic control in the CSII group the Steno group showed greater deterioration of retinopathy than in conventionally treated patients over the first year. This transient deterioration in diabetic retinopathy after initiation of improved glycaemic control was also reported by the Kroc, Oslo, Aarhus (Beck-Nielsen 1990, Olsen 1987) and Stockholm studies, reversing only after two years follow-up. The SDIS study demonstrated a reduced risk of decreased visual acuity and serious retinopathy requiring laser photocoagulation with intensive therapy. In contrast, the Oxford Aylesbury Study revealed comparable rates of retinopathy progression after two years in 74 diabetic patients randomly allocated to conventional care or multiple insulin injections (Holman, 1983). The Dallas Diabetes Prospective Trial (Friberg 1985, Rosenstock 1986) demonstrated significantly less retinopathy progression, measured by macular aneurysm counts and EDTRS grading in 30 T1DM patients on intensive insulin therapy compared to 24 conventionally treatment patients (HbA_{1c} 7.4% vs 10.2%). These results are summarised in a meta-analysis by Wang (1993) in which intensive therapy was reported to reduce HbA_{1c} by 1.4% (95%CI 1.1-1.8), with an OR of 0.49 (95%CI 0.28-0.85) for retinopathy and OR 0.34 (95%CI 0.20-0.58) nephropathy progression after more than 2 years of intensive therapy. The intervention studies listed above were limited by small sample sizes and short durations of follow-up. None of the studies commenced early in the course of diabetes before the initial development of complications.

Nephropathy

Retrospective and prospective trials have consistently demonstrated beneficial effects of intensive glucose control on microalbuminuria progression and hyperfiltration in diabetic patients. 32% patients treated with multiple insulin injection therapy developed nephropathy in the Malmo study compared to 56% on once daily insulin injections (Johnsson, 1960), and nephropathy incidence was doubled with poor glycaemic control in the Pirart (1978) study. Beneficial renal effects were most evident in subjects with mildly elevated urinary albumin levels in the Steno (Feldt-Rasmussen 1986, Deckert 1983), Kroc, Dallas, Stockholm (Reichard, 1989), Oslo (Dahl-Jorgensen, 1988) and Arrhus trials. Indeed after five years of follow up, the Stockholm study revealed an average increase in urinary albumin excretion rate from 74.3 to 239.9 μg/min in the regular treatment group but no change in the intensified conventional treatment group ($p<0.05$). Most studies failed to demonstrate alterations in urinary albumin excretion, irrespective of treatment group or level of control, when urinary albumin excretion rates were normal at entry (Kroc 1985, Beck-Nielsen 1990, Deckert 1983, Rosenstock 1987) and reversal of significant renal disease with intensive glucose control has not been demonstrated (Tamborlane 1982, Viberti 1983).

Neuropathy

An association between glucose control and neuropathy has been demonstrated conclusively. Motor, sensory and autonomic nerve function were significantly improved with intensive glucose control in studies by Young (1986), Pirart (1978), Service (1985) and Troni (1984). Motor nerve conduction velocity increased significantly (average increase 2.5 m/s) after six weeks of insulin pump therapy in the Dallas study and after 36 months in the Stockholm study. The latter finding persisted to 7.5 years follow-up. Observations regarding vibration perception threshold, sensory action potential and autonomic nervous system function (ANS) were less conclusive. Vibration threshold measures were unchanged irrespective of therapy group and glucose control in the Steno, Stockholm and Oslo studies but improvements with intensive insulin therapy were seen in Oxford and Aarhus studies (Woolf, 2000).

3.2.4: Landmark Studies of Glucose Control and Complications in Type 1 diabetes

The Diabetes Control and Complications Trial (DCCT), a ten-year multicentre trial, provided conclusive proof of the relationship between glycaemic control and diabetes complications in 1993. Randomisation of 1441 type 1 patients, mean age 27 years, to conventional treatment with one or two daily insulin injections or multiple insulin injections/insulin pump therapy produced

significantly different HbA_{1c} measures (8.9% cf 7.2%) over a mean 6.5 years follow up (9300 patient-years observation). Half of the patients had diabetes for less than 5 years at entry into the study and had no evidence of retinopathy or nephropathy. The remaining patients had diabetes for less than 15 years and early background diabetic retinopathy and urinary albumin excretion <200mg/24 hrs. The goals of intensive therapy included preprandial blood glucose concentrations <180mg/dL, a weekly 0300 measurement greater than 65mg/dL and HbA_{1c} measured monthly in the non-diabetic range.

The cumulative incidence of sustained retinopathy did not differ between therapy groups in the primary prevention cohort until three years whereas in the secondary intervention cohort higher cumulative incidence of sustained progression of retinopathy occurred in the intensive treatment group over the first year. This trend was reversed at 36 months. Overall, the adjusted mean risk of sustained retinopathy development was reduced with intensive therapy by 74% in the primary prevention cohort and 53% in the secondary intervention cohort. This risk reduction with intensive therapy was consistent among subgroups based on age, gender, diabetes duration, body weight, blood pressure, screening HbA_{1c} and albuminuria.

Microalbuminuria (>40mg/24 hours) was reduced by 34% and 43% and clinical neuropathy (abnormal neurological examination plus either abnormal nerve conduction in at least two peripheral nerves or abnormal autonomic nerve testing) by 69% and 57% in the two cohorts respectively. Non significant reductions in macrovascular disease (41%) and hypercholesterolaemia (34%) were also observed. No difference in mortality was seen between treatment groups within this study. Severe hypoglycaemia was three times commoner in the intensive treatment groups but no difference in quality of life was observed.

The Stockholm Diabetes Intervention Study (Reichard, 1988-1993) confirmed these results in 96 T1DM patients with non-proliferative retinopathy over 5 years.

Table 3.1 DCCT Trial Summary Results: 6-Year Risk of Microvascular Disease (Cerveny 98)

Disease State	Intensive (%)	Normal (%)	ARR (%)	NNT (n)
Retinopathy				
• Primary	1.2	4.7	3.5	29
• Secondary	3.7	7.8	4.1	24
Nephropathy				
• Primary	2.2	3.4	1.2	83
• Secondary	3.6	5.7	2.1	48
Clinical neuropathy				
• Primary	3.1	9.8	6.7	15
• Secondary	7.0	16.1	9.1	11

3.2.5: Landmark studies of glucose control and complications in type 2 diabetes:

Four randomised controlled clinical trials have examined the correlation between glycaemic control and complications in T2DM – the University Group Diabetes Program (1982), the Kumamoto study (Ohkubo 1995), Veterans Affairs Cooperative study (Abraira 1995, Levin 1996, Emanuele 1996) and the United Kingdom Prospective Diabetes study (Turner 1996-1998, UKPDS 1998-2003). A summary of the design and principal findings of these studies is provided below.

The University Group Diabetes Program (UGDP)

The UGDP prospective data demonstrated no benefit of glycaemic control on rates of retinopathy or proteinuria with insulin or sulphonylurea therapy in 1021 newly diagnosed patients (mean age 53 years) over an average 12.5 year follow-up and reported increased cardiovascular and all-cause mortality with tolbutamide and phenformin therapies causing their discontinuation at seven years (Knatterud, 1978). Insulin atherogenicity and increased risk of ventricular fibrillation (Stout 1993, Genuth 1990) with sulphonylurea therapy were postulated but small numbers, absence of a reliable chronic glycaemia measure, infrequent FBG measurements and small differences in glucose control between intensive and regular treatment groups prevented reliable conclusions. Subsequent analyses also revealed discrepancies in the sex ratio of cardiovascular deaths in placebo subjects in this study

and isolated excess CVS mortality to a small group of poorly controlled tolbutamide treated diabetic patients. The study was criticised too for lack of power, omission to collect smoking history data and inclusion of people at high risk for CVD. The cessation of the oral agent arms in 1969 was criticised because all centres did not experience increased mortality and an insufficient number of outcomes occurred to make definitive conclusions (Cerveny, 1998).

The Kumamoto Study

A small prospective randomised controlled trial of 110 T2DM lean Japanese patients demonstrated reduced onset and progression of microvascular complications with intensive glucose control using multiple insulin injections (HbA_{1c} 7.1%) compared to conventional insulin therapy (HbA_{1c} 9.4%) over a mean 6 year follow-up. A primary prevention group, those without baseline retinopathy and urinary albumin excretion less than 30mg/24hours, and secondary intervention group with simple retinopathy and urinary albumin excretions between 30-300mg/24hours were included. The clinical goal of the CIT group was to show no symptoms of hyperglycaemia or hypoglycaemia and fasting blood glucose concentration as close to <140mg/dL as possible. The goal of the MIT group was to maintain FBG <140mg/dL, 2-hour postprandial blood glucose concentration <200mg/dL, HbA_{1c} <7.0% and mean amplitude of glycaemic excursions <100mg/dL. Intensive glucose control significantly reduced the progression of retinopathy (7.7 vs 32% p=0.039) and neuropathy (7.7 vs 28% p=0.049) with significant differences in nerve conduction velocities also seen between the two groups. Risk reductions in this study were comparable with those in DCCT, thereby supporting the hypothesis that intensive glycaemic control reduces microvascular complications in both types of diabetes. Several study limitations exist, however. The patient population in this study was different to that usually encountered in the UK or US. Patients were younger (40-50 years), leaner (mean BMI 20kg/m^2), more insulin sensitive (approx 20-25 units/day) and had no hyperlipidaemia, hypertension or ECG abnormalities. Some of the study patients may have had absolute insulin deficiency in contrast to the hyperinsulinaemia found in type 2 patients in the UK and US. The number of CVD events in both groups was also small (only 5 events or <1% per year), making it difficult to reach a conclusion from the lack of differences in the rate of combined CVS events in the study. The principal findings of the Kumamoto study are summarised in table 3.2 overleaf.

Microvascular complications were reduced with fasting plasma glucose levels below 7.8 mmol/l in an epidemiological study of Pima Indians (Nelson,1993), and the results were confirmed in a similar study in whites using 2-hour oral FPG tolerance data (Jarrett, 1984).

Table 3.2 : Principal results of the Kumamoto study (Cerveny, 1998)

Disease State	MIT (%)	CIT (%)	ARR (%)	NNT (n)	P value
Retinopathy					
• Primary	7.7	32	24.3	4.1	0.039
• Secondary	19.2	44	24.8	4.0	0.049
Nephropathy					
• Primary	7.7	28	20.3	4.9	0.032
• Secondary	11.5	32	20.5	4.9	0.044

The effect of glucose control on macrovascular disease in diabetic patients remained controversial. Little direct evidence of a relationship existed but epidemiological studies of the general population demonstrated an increased risk of cardiovascular disease with concentrations of fasting plasma glucose (FPG) or HbA_{1c} just above the normal range (Fuller 1983, Balkau 1999). Improvements in lipid metabolism with better blood glucose control were probably the most consistent findings relevant to the risk of cardiovascular disease but studies of the effects on erythrocyte adhesion and platelet function remained inconclusive.

The Veterans Affairs Cooperative Study on Glycaemic Control and Complications (VA CSDM)

The Veterans Affairs Cooperative Study on Glycaemic Control and Complications Feasibility Study randomised 153 men aged 40-69 years with poorly-controlled T2DM (HbA_{1c}>6.5% of insulin or maximal oral sulphonylurea therapy) to intensive (HbA_{1c} goal 4-6.1%) or conventional (HbA_{1c} <2sd above the mean) insulin therapy arms. Standard therapy comprised diet, exercise and one insulin injection daily, with addition of a second injection if treatment goals were not met. Intensive therapy consisted of a stepped regimen with four successively increasingly intense phases plus home blood glucose monitoring. Phase 1 consisted of one injection of intermediate or long-acting insulin, phase 2 included additional once-daily glipizide. Phase 3 discontinued this glipizide and used two daily insulin injections whilst phase 4 comprised multiple daily insulin injections. Despite a 2.1% absolute HbA_{1c} difference, no significant difference in cardiovascular events occurred over the mean 27 month (range 18-35 month) follow up period. A total of 61 new cardiovascular events occurred in 40 patients during this study. 35 events occurred in 24 patients (32%) in the intensive arm and 26

events occurred in 16 patients (20%) in the standard arm (p=0.10). In a Cox regression analysis on time to cardiovascular events there was a borderline trend toward increased cardiovascular events in patients with a lower HbA_{1c}. A sustained decrease in serum triglyceride and total cholesterol levels was noted with intensive glycaemic therapy with a significant increase in the LDL-cholesterol /apolipoprotein B ratio (Emanuele, 1996). HDL, LDL, BP and BMI were unchanged (Abraira, 95).

The United Kingdom Prospective Diabetes Study (UKPDS)

Set against this background, the UKPDS was the largest prospective randomised controlled intervention trial of T2DM ever conducted. Its aim was to determine whether improved glucose control with intensive pharmacological therapy would reduce microvascular and macrovascular diabetic complications, and to evaluate whether different therapies offered specific advantages or disadvantages (sulphonylurea toxicity/insulin atherogenicity). 5102 newly diagnosed type 2 patients, aged 25-65 years inclusive, were recruited from 23 UK hospital centres between 1977 and 1991. Median age at diagnosis was 53 years, median FPG 11.9 mmol/l and mean body mass index 28.9 kg/m^2. 58% were male, 82% caucasion, 10% indo-asian and 8% afro-caribbean. 50% patients were obese, and hypertension (defined as systolic pressure >160 and diastolic pressure >90mmHg or current antihypertensive medication) was present in 37% males and 52% females. 50% of patients had clinical evidence of diabetes complications at diagnosis, 8% had cardiovascular disease, 55% had retinopathy and 18% had microalbuminuria (>50mg/L).

Patients were seen monthly by a dietitian for three months and advised to follow a low-fat, high carbohydrate, high fibre diet with energy restriction in obese subjects. After three months 4209 asymptomatic patients with a mean plasma glucose concentrations of 6.1-15.0 mmol/l were randomised to either conventional therapy with diet alone or intensive therapy with sulphonylurea, insulin or metformin in overweight patients. Patients attended morning clinics every three or four months. The primary goal in the intensive therapy group was to maintain FPG <6mmol/l whilst in the conventional group FPG maintenance <15mmol/l without hyperglycaemia symptoms was sought. An unbalanced randomisation was employed to allow comparison of several different therapies. Two different pharmacological approaches were thus evaluated: improvement of glucose control by increasing insulin supply, comparing patients on intensive sulphonylurea or insulin therapy with those on conventional therapy, primarily with diet; and enhancing insulin sensitivity in obese subjects by comparing patients allocated to intensive metformin therapy with those allocated to conventional therapy.

Three aggregate endpoints were used to assess differences between the conventional and intensive therapies: any diabetes related endpoint (sudden death, death from hyper or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, retinopathy, vitreous haemorrhage, blindness or cataract extraction), diabetes related death (MI, CVA, PVD renal disease, hyperglycaemia, hypoglycaemia, sudden death) and all cause mortality. Analyses were performed on an intention to treat (ITT) basis.

Considerable variation in response to dietary therapy occurred in UKPDS. 86% patients became symptom-free after three months but only 867 patients (17%) achieved FPG <6mmol/l (50% of those with FPG 6-8 mmol/l and 10% with FPG 16-22 mmol/l) and in 67% of these patients FPG subsequently increased to >6mmol/l in 3 years. Mean weight loss over this initial three month period was 5kg (12lb). Patients presenting with an FPG 12 mmol/l needed to lose 30% of their ideal body weight to attain FPG <6 mmol/l within three months. This rate of weight loss was not sustained over the following year and if diet was only restricted sufficiently to maintain initial weight loss FPG levels increased. Reduction of energy intake thus appeared to be as important as weight loss in determining FPG.

Blood glucose rose inexorably with time during the UKPDS with an average 1% HbA_{1c} increase every five years, irrespective of treatment group. Pharmacological monotherapy did not maintain FPG < 6 mmol/l in the intensive therapy group and combination therapy was required. Equally 80% of patients in the dietary control group required one or more pharmacological agents to maintain FPG <15 mmol/l. Specific drug effects were thus confounded by drug crossover and substitution but an average difference of HbA_{1c} 0.9% and FPG 1.7 mmol/l was maintained between conventional and intensive treatment policies.

This intensive glucose control produced a 12% reduction in any diabetes related endpoints, a 25% reduction in microvascular disease, a 21% reduction in retinopathy progression, a 24% reduction in cataract extraction and a borderline non-significant 16% reduction in MI (p=0.052). Extrapolation of these results revealed that for each 1% HbA_{1c} increase, patients sustained a 37% increase in microvascular disease, 23% increase in cataract extraction, 27% increase in diabetes related deaths, 16% increase in myocardial infarction and 79% increase in peripheral vascular disease. Progression of subclinical surrogate variables of microvascular disease also decreased in agreement with other studies of blood glucose control. Numbers needed to treat over ten years to avoid one diabetes related endpoint by intensive glucose control were 20, to avoid one diabetes related death, 91, to avoid one myocardial infarction, 37 and to avoid one stroke, 167. The median complication-free interval was 1.3 years longer in the intensive therapy group than the conventional group. These

results mirrored the DCCT T1DM data that intensive glycaemic control reduces microvascular complications. Epidemiological analysis of these studies revealed no evidence of a glycaemic threshold above a normal HbA_{1c} clearly indicating that normal blood glucose values should be sought in T2DM management. The effect of glycaemic control on macrovascular disease remained unclear.

No clear differences between intensive therapies were demonstrated but in contradistinction to UGDP neither sulphonylureas or insulin produced demonstrable adverse effects on CVS outcomes despite higher fasting plasma insulin levels in the latter group. Glucose intensification did produce adverse effects, principally weight gain and hypoglycaemia (major hypoglycaemia 0.1% diet, 0.6% SU, 2.3% insulin; minor hypoglycaemia 1%, 11%, 18%, 37% per year), but benefits of glycaemic control outweighed these risks. Quality of life was significantly worsened by diabetes complications in UKPDS but intensive glucose policies produced no such effect (UKPDS 37). Indeed improved glycaemic control has been found recently to be associated with favourable mood and well-being in T2DM (Van der Does, 1998).

Metformin was included as a primary randomisation option in overweight UKPDS patients from 1977. 753 overweight patients with newly diagnosed T2DM were included in a randomised controlled trial of conventional policy, primarily with diet alone versus intensive glucose control with metformin, aiming for FPG below 6 mmol/l over a median duration of 10.7 years. Secondary analyses compared 342 metformin patients with 951 overweight patients allocated to intensive blood glucose control with chlorpropamide, glibenclamide or insulin. Median HbA_{1c} was 7.4% with metformin and 8.0% in the conventional treatment group. Patients assigned to metformin therapy had a 32% lower risk ($p=0.0023$) of developing diabetes-related endpoints, a 39% lower risk ($p=0.010$) of MI and a 41% lower risk ($p=0.032$) of stroke compared with conventional treatment groups. Diabetes-related deaths and all-cause deaths were also significantly reduced. Metformin significantly reduced weight gain, fasting plasma insulin concentrations and hypoglycaemia episodes more than sulphonylureas or insulin therapies.

Decreased PAI-1, fibrinolysis inhibition and reduced systemic methylglyoxal concentrations were postulated as mechanisms for the potential macrovascular benefits with metformin but contradictory subanalyses results suggested caution. Combined metformin and sulphonylurea therapy in 537 obese and normal weight patients increased diabetes-related deaths by 96% and all-cause deaths by 60% compared with sulphonylurea therapy alone. Epidemiological analysis and meta-analysis did not substantiate this finding and a small numbers effect was postulated. Higher cardiovascular mortality with metformin and sulphonylurea combination therapy was detected more recently in a

Swedish observational study (Olsson,2000) but thought to be secondary to more aggressive diabetes in patients selected for such treatment. Further research of this effect is clearly required, however.

3.3: Glucose Control and Macrovascular Disease

3.3.1: Cross-sectional, prospective observational and non-randomised intervention studies

Many XS, prospective observational and non-randomised intervention studies have investigated the relationship between glucose control and CVD risk in diabetic and non-diabetic patients. (Ostrander 1965, Framingham 1970, Gordon 1972, Kannel 1979, Stamler 1979, Fuller 1980 1983, Jarrett 1982, Yano 1982, Cruz-Vidal 1983, Welborn 1984, Hillson 1984, Barrett-Connor 1984, Eschwege 1985, Pyorala 1985, Butler 1985, Pan 1986, Hanefeld 1991, Morrish 1991, Manson 1991, Fontbonne 1992, Singer 1992, Knuiman 1992, Balkau 1993, Laakso 1993, Uusitupa 1993, Fu 1993 and Kuusisto 1994, Moss 1994, Anderson 1995). Early observational studies were limited by small patient numbers, infrequent events and short follow-up periods. Accurate measurement of the exposure and outcome was problematical with cross-sectional designs, and survival bias likely.

Evidence for the absence of a glucose threshold for macrovascular risk was provided by large-scale prospective epidemiological studies. In the Paris Prospective study (Eschwege,1985) CVD mortality was significantly higher in the top 20% for glucose and insulin, and in the top 5% for PPG in the Whitehall study (Fuller 1980, Jarrett 1985). Similarly in the Rancho Bernardo study (Barrett-Connor 1984) of 3458 subjects with FPG <7.8 mmol/L IHD mortality rates increased 2-fold in men as their FPG increased from 5 to 7mmol/L. The Chicago heart study (Pan, 1986) demonstrated that 1-hour blood glucose levels were predictive of 9-year mortality whilst the British Regional Heart study (Perry, 1994) demonstrated significantly more IHD in subjects with glucose levels above the 80^{th} centile. Random glucose testing was found to predict CHD in women but not men in the Framingham study (Wilson, 1991) and 1-hour glucose was predictive of CHD in the Tecumseh (Butler, 1985), Honolulu (Donahue, 1987) and Helsinki policeman studies (Pyorala, 1985).

Baseline FPG, 5 year FPG/HbA_{1c} were found to be associated with CVD mortality in a Finnish 10 year study of 133 newly diagnosed diabetics (Uusitupa, 1993), HbA_{1c} was a strong predictor of CAD mortality in 229 elderly T2DM patients monitored for 3.5 years (Kuuisto,1994) and in a study of 411 newly diagnosed T2DM subjects FPG was a significant risk factor for CVS (p=0.0006) and IHD (p=0.03) mortality over 7.4 years (Andersson, 1995). Similarly in a trial of younger T2DM subjects (mean age 54 years), a significant correlation between poor metabolic control and CVS mortality risk (Gall,1995) was seen. The WESDR study (Klein,1995) revealed stronger associations

between HbA_{1c} and CHD mortality in T1DM than T2DM patients; a 1% rise in HbA_{1c} CVS mortality in younger onset diabetic subjects was associated with a 20% rise in IHD mortality in T2DM subjects and a hazard ratio of 1.10 was reported in older-onset diabetes for every 1% HbA_{1c} increase. In the Lehto study (1996) involving 1059 patients with T2DM followed for 7 years high FPG levels (>13.4mmol/L) were associated with a 2-fold increase in the risk of CHD mortality and morbidity. The risk was further increased to 3-fold in patients who had high FPG, low HDL, low HDL-cholesterol ratio or high triglycerides. The association between hyperglycaemia and CVD in this study was found to be independent of conventional risk factors but this finding was not confirmed by the studies of Wingard (1987), Gall (1995), Laakso (1993) and Andersson (1995). In the Munich General Practice Project HbA_{1c} was a major determinant of CVD-related mortality in 290 T2DM patients. Similar results were seen in the studies by Hadden (1997), Hellman (1997) and Wei (1998).

A progressive relationship between CVD and glucose below the diabetic threshold was reported in several studies (Lowe 1997, Balkau 1999, Singer 1992 Haffner 1990) and a recent meta-analysis of non-diabetic populations by Coutinho reported a continuous increase in CVD risk with glucose levels above 4.2mmol/L suggesting that CVD risk begins in the prediabetic state. These results are supported by the EPIC study (2001) and Wareham. An increased prevalence of CVD with IGT has also been reported in many studies. The Da Quing study (Pan, 1993) found 4% of IGT patients had ECG abnormalities compared with 0.4% controls, Ohlson (1989) reported an increased CVD prevalence in IGT males aged 67 years and Rewers (1992) observed a 2-fold increase in CHD in non-Hispanic white IGT individuals compared to controls. Saydah confirmed a mortality gradient associated with abnormal glucose tolerance, ranging from a 40% greater risk in adults with impaired glucose tolerance to a 110% greater risk in adults with clinically evident diabetes. Finally the Whitehall (Fuller, 1980) and Hisayama (Fujishima, 1996) studies demonstrated increased CVD mortality with IGT versus NGT.

3.3.2: Systematic review and meta-analyses

The relationship between blood glucose and incidence of CVD was assessed recently in a systematic review and metaregression analysis of 95,783 people with 3,707 cardiovascular events over 12.4 years. A graded relationship between fasting and postprandial blood glucose level and subsequent 12 year occurrence of cardiovascular events was demonstrated. Compared with a glucose level of 4.2 mmol/l, a fasting and 2-hour glucose level of 6.1 and 7.8 mmol/l were associated with a cardiovascular relative risk of 1.33 (95% CI 1.06-1.67) and 1.58 (95% CI 1.19-2.10) respectively. The progressive relationship between blood glucose levels and cardiovascular risk were found to

extend below the diabetic threshold in this study. This was explicable as glycaemic thresholds for diabetes have always been selected to identify people at risk for retinal and renal disease without regard to CVS risk.

Relationships between glucose levels and CVD are inconsistent in the literature. Specific effects and mechanisms of hyperglycaemia on CVD in diabetic patients are unclear and separating out the primary cause and effects of glucose from other features of the metabolic syndrome remains complex (Gerstein, 1996). Although no published studies have demonstrated a negative effect of glucose control on macrovascular complications many have failed to establish hyperglycaemia as an independent risk factor for CVD. The NIDDM Patient Outcomes Research Team revealed no association between HbA_{1c} and CVD in 1539 patients in a cross-sectional prevalence study in 1997 (Meigs, 1997) and similar conclusions were reached in studies of T1DM patients (Lloyd, 1996).

3.3.3: Prospective clinical trial data

The results of prospective clinical trial data are equally inconsistent suggesting clinical reduction in cardiovascular disease but with little data of statistical significance to conclusively support prevention of CVD development or progression with intensive glycaemic control. The UGDP failed to show an effect of variable insulin doses on CVD whilst the DCCT and Kumamoto study showed a trend toward improved CVS outcomes in the intensively treated group. Numbers of patients and events in these two studies were insufficient to achieve statistical significance. UKPDS also revealed a borderline significant trend toward reduction in nonfatal MI with intensive glucose control. The use of metformin in newly diagnosed obese patients resulted in significant reduction in MI but the addition of metformin to sulphonylurea failures appeared to increase cardiovascular events. In contrast the VACSP prospective study on established T2DM patients revealed a trend towards increased CVS events with intensive therapy. DIGAMI (Malmberg,1995) demonstrated a significant improvement in clinical outcomes with intensive insulin therapy in the immediate and extended post-MI period in 620 T1DM and T2DM subjects over an average 3.4 year follow-up period. The 28% reduction in myocardial events with intensive intravenous insulin therapy compared with conventional therapy that occurred is thought, however, to reflect effects of insulin in preventing myocardial damage more than effects of improved glucose control. This was illustrated in a subsequent meta-analysis in non-diabetic patients where decrease in recurrent MI in the glucose/ insulin/potassium-treated patients was 29%.

3.3.4: Future studies

As a result of the inconsistencies in the evidence relating to glucose and CVD three further studies have been commenced.

The VACSP Glucose Control and Cardiovascular Complications in Diabetes Mellitus Type 2 was initiated in December 2000 to examine the effects of conventional versus intensive glucose control on development of CVD hard endpoints, including death from CV disease, PVD, MI, stroke and other clinical events in 1700 patients in 20 centres over 5-7 years. An HbA_{1c} separation of >1.5% is sought.

The NIH study: the Action to Control CV Risks in Diabetes (ACCORD) trial includes 10000 patients with type 2 diabetes who will be followed for 4-6 years in 59 clinical networks. This study will examine the effects of glucose control, blood pressure control and lipid therapy directed at reducing triglycerides and increasing HDL. Conventional glucose control will be defined as HbA_{1c} <7.5% and intensive <6%. The practicality of this approach will be tested in a 1-year pilot component.

A third trial the Bypass Angioplasty Revascularization Investigation 2 (BARI 2) trial will examine the effects of different approaches to glucose control in patients with established CV disease and will compare the effects of glucose control with either agents that increase insulin levels (including SU and exogenous insulin) and agents directed at increasing insulin sensitivity (including metformin, TZD and short-acting insulin secretagogues). This is an important study given the uncertainty about the relative effects of insulin resistance and hyperinsulinaemia in the development of CV disease.

3.4: Glucose Management Strategies

3.4.1: Dietary modification

Dietary modification is the mainstay of treatment for T2DM. Nutritional advice aims to achieve ideal body weight (BMI<25), reduce CVS risk and maintain glucose homeostasis. A diet consisting of fibre-rich carbohydrates (>50% calories), protein (<20% calories), fats (<30% calories) and five daily fruit or vegetable portions is recommended (DUK). Saturated, poly and monounsaturated fats should each be restricted to <10%, sucrose to <25 g/day and sodium to <6 g/day. Specialist diabetic foods should be avoided and alcohol reduced to <2 units/day. Antioxidants may also reduce diabetes complications.

Dietary advice can produce dramatic improvements. UKPDS demonstrated a 3.8 mmol FPG reduction, 2% HbA_{1c} reduction and 5% reduction in body weight (approximately 3.5-4.0 kg) with dietary advice over three months. This weight loss was maintained for over ten years in the conventional therapy group. Enhancement of β-cell function and insulin action appear to be responsible for improvements in glucose control. In many studies the results of dietary therapy have been more disappointing and sustained weight loss not achieved. Intensified regimens including modified fasting periods during hospital admissions have improved short-term glucose control and dyslipidaemia considerably but the long-term benefits have been poor (Wolffenbuttel, 1993). Diabetes prevention studies have demonstrated favourable results with diet, however (DPP, 1999, DPS, 2001)

Weight loss is associated with beneficial effects (NIH, 1998) on hyperglycaemia (Maggio 1997, Wannamethee 1999), dyslipidaemia, hypertension and significant improvement in hepatic glucose output and peripheral insulin resistance (Everson, 1998). These improvements occur with modest weight loss (10-15% of initial weight).

3.4.2: Physical Activity

Few definitive studies examining the effects of exercise in T2DM have been successfully undertaken Difficulties separating diet and exercise effects, heterogeneity of initial hormonal-metabolic status, T2DM deterioration and lack of motivation of patients to participate in training programmes lasting more than 3-6 months are commonly cited. Overall exercise appears to improve insulin sensitivity, reduce hyperglycaemia and hyperinsulinaemia (Kemmer, 1997) and is associated with reduced incidence of T2DM (Chakravarthy, 2002).

3.4.3: Pharmacological Approaches

A. Sulphonylureas

Sulphonylureas are sulphonamide derivatives which reduce both fasting and postprandial blood glucose by enhancing insulin secretion in patients with functional pancreatic tissue. Mechanisms underlying sulphonylurea-related insulin secretion are controversial. These agents bind to specific receptors on the β-cell plasma membrane causing potassium channel closure, inhibition of potassium efflux and membrane depolarization, thus inducing voltage dependent calcium channel opening, calcium influx, activation of cytoskeletal systems via protein kinase phosphorylation and exocytotic extrusion of insulin secretory granules. Glucose-induced insulin secretion occurs via glucose entry and metabolism in the β-cell, ATP synthesis, closure of ATP linked potassium channels, membrane depolarization and activation of insulin secretion routes. Sulphonylurea receptors are closely related to ATP linked potassium channels and these agents thus enhance both glucose induced insulin secretion and insulin responses to non-glucose stimuli.

Sulphonylureas are safe effective agents with an overall frequency of adverse events of 2-5%. The commonest adverse event is hypoglycaemia but rarer side effects include thrombocytopenia, marrow aplasia, agranulocytosis, haemolytic anaemia, rashes, pruritus, erythema nodosum, erythema multiforme, Stevens Johnson syndrome, purpura, exfoliative dermatitis, hypersensitivity, jaundice, cholestasis, granulomatous hepatitis, water retention, vasculitis and vasomotor changes. Increased CVS mortality was reported initially (UGDP, 1970) with these agents but later dispelled by UKPDS which demonstrated no excess macrovascular risk with glipizide or glibenclamide. UKPDS demonstrated a mean weight increase with sulphonylurea therapy of 2.3 kg over ten years.

The kinetic-dynamic relations of sulphonylurea agents are complex. Glucose, as the major stimulant of insulin secretion, obscures the drug-response relationship; absorption is reduced with hyper-glycaemia, β-cell function improves with low glucose levels, chronic use leads to desensitization of the insulin response and decreasing drug effects occur at high doses. Primary sulphonylurea failure occurs in patients with deficient insulin secretory capacity (10-20%) and β-cell exhaustion produces secondary failure in 44% patients over 6 years. Increased failure rates are seen with higher glucose concentrations, lower β-cell reserve and younger age. Treatment with equivalent doses of sulphonylureas gives similar results. The second-generation sulphonylureas are reported to decrease FPG by 60mg/dL (Palumbo, 2001).

B. Meglitinides

Repaglinide, a meglitinide analogue, differs from sulphonylurea both in molecular structure, profile of action and excretion. As a benzoic acid derivative it has a high binding affinity for ATP-sensitive K+ channels on the beta cells acting at a different site from sulphonylurea to stimulate insulin release, with more rapid onset and shorter duration of action. It is less effective than sulphonylureas and metformin in reducing FPG and HbA_{1c} levels but in accordance with its mode of action and short plasma half-life has greatest effect on postprandial glucose levels. Its primary adverse effect is hypoglycaemia.

C. Biguanides

Biguanide agents are aminoguanidine derivatives which decrease hyperglycaemia by multifactorial peripheral metabolic mechanisms some of which are poorly understood. Increased muscular glucose utilization and decreased hepatic gluconeogenesis (Cusi, 1998) ameliorate insulin resistance and these insulin-mediated effects occur predominantly at postreceptor sites. Glucose utilization is also increased directly via free fatty acid oxidation. Increased insulin action reduces hyperinsulinaemia (UKPDS 24, 1998) and contributes to reduced lipid levels, blood pressure, weight stabilisation (Bailey 1992, Dunn 1995), decreased plasminogen activator inhibitor type 1 and thus increased fibrinolysis. Decreased intestinal absorption reduces hyperglycaemia but may induce vitamin B12 or folic acid deficiency and gastrointestinal side-effects. Gluconeogenic precursor concentrations (alanine, lactate) are increased.

Metformin, the commonest biguanide in clinical use, is incompletely absorbed from the small intestine, oral bioavailability is approximately 50-60% and plasma half-life 1.5-4.5 hours. Rapid elimination by active tubular secretion occurs with 90% excreted unchanged in the urine within 12 hours. Metformin exerts an antihyperglycaemic effect in 80% of patients, with fasting blood glucose reductions of 1.4-3.9 mmol/l and HbA_{1c} reductions of 0.8-2.0%. Efficacy equates to insulin and sulphonylurea therapy but additional beneficial effects on weight, lipids, hypoglycaemia and macrovascular disease are reported (UKPDS 33 1998, Reaven 1999). Severe renal, hepatic, CVD and respiratory disease contraindicate use of metformin due to excess risk of lactic acidosis.

D. Alpha glucosidase inhibitors

α-glucosidase agents competitively inhibit intestinal brush border α-glucosidases delaying digestion and absorption of carbohydrates and reducing prandial hyperglycaemia excursions. Acarbose is non-insulotrophic, minimally absorbed with beneficial effects on weight and lipids (reduction of postprandial hypertriglyceridaemia and total cholesterol). HbA_{1c} reductions of 1.5% fasting plasma glucose 52 mg/dl and one-hour postprandial glucose concentrations 63mg/dl are reported and acarbose addition to other regimens induces a sustained further HbA_{1c} reduction of 0.5% (UKPDS 44, 1999). Polysaccharide and disaccharide hydrolysis by large intestinal bacteria increase colonic fluid secretion and metabolism of breakdown products producing flatulence, diarrhoea and abdominal pain at treatment onset. Elevated hepatic transaminases are also reported. α-glucosidase inhibitors are contraindicated with inflammatory or obstructive bowel disease and cirrhosis.

E. Thiazolidinediones

Thiazolidinediones (TZD) are a new class of oral antidiabetic agent which function as activating ligands for PPARy steroid nuclear receptors. PPARy receptors agonists preferentially improve insulin action by enhancing insulin receptor tyrosine kinase activity and promoting gene transcription events, enhancing control of glucose production, transport and utilization in skeletal muscle, liver and adipose tissue. The precise mechanism of action remains unclear. TZDs bind to PPARy nuclear receptors and heterodimise with retinoid X receptors activated by 9 cis retinoic acid. The heterodimer receptor binds to PPRE ligand motives on cellular DNA to control expression of target genes. Altered expression of enzymes including fatty acid synthase and lipoprotein lipase results. TZDs reduce insulin resistance, fasting and post-prandial hyperglycaemia, serum insulin, proinsulin, split proinsulin, NEFAs, triglycerides and weight, and may provide beneficial long-term effects for the pancreas by maintaining β-cell function. Increased insulin-stimulated glucose disposal, glucose uptake and metabolism, increased lipid clearance and suppression of hepatic glucose production also occur. TZD use is associated with increased LDL cholesterol, probably as a result of larger nonatherogenic LDL particle size and a rise in high density lipoprotein cholesterol. Reduction in urinary albumin excretion with rosiglitazone in type two patients suggests a potential beneficial effect of the agent in the treatment and prevention of renal and vascular complications. Adverse effects include anaemia, oedema and hypoglycaemia but no hepatocellular toxicity is reported. The TZDs are reported to be less effective as monotherapy than sulphonylureas and metformin in decreasing FPG and glycated haemoglobin levels (Palumbo, 2001).

F. Rapid Acting Insulin

Humalog or lispro insulin, an insulin analogue with inversion of proline-lysine amino acid sequences at position 28/29 on the β-chain, has a pharmacokinetic profile that more closely mimics physiological insulin response. Its faster onset and shorter duration of action than regular insulin results in more effective control of mealtime glycaemia.

3.4.5: Polypharmacy

Dietary modification and exercise have traditionally been regarded as the initial management steps for patients with T2DM. Later with progressive failure of insulin secretory capacity, oral agents are used to promote insulin secretion, improve insulin action in peripheral tissues or delay meal carbohydrate absorption. In recent years therapeutic combinations have been used to target diabetes pathophysiology at multiple points where insulin secretion is moderate. Nevertheless with time and inadequate attention to lifestyle most patients become truly insulin deficient with insufficient secretory capacity to drive insulin action in target tissues despite secretagogue and sensitizer therapy. Insulin use is then required.

Review of reported monotherapy studies of oral agents document that few patients randomised achieve near normal glucose targets regardless of the agents selected. The progressive requirement for multiple therapies in T2DM management was clearly demonstrated by the UKPDS. Each mono-therapy increased the proportion of patients who attained HbA_{1c} below 7% two to three fold compared with dietary therapy alone. However, the progressive deterioration of diabetes control was such that after three years 50% of patients attained this goal with monotherapy and by nine years this declined to 25%. The majority of patients required multiple therapies to attain glucose targets in the long term and indeed 22% of patients randomised to metformin and 30% of patients randomised to sulphonylurea needed insulin therapy by six years (UKPDS 24 1998, UKPDS 49 1999).

3.4.6: Insulin Use

Patients are generally adverse to insulin particularly as first line therapy. Many are asymptomatic in the presence of hyperglycaemia, and believe insulin will not improve their wellbeing (Wolffenbuttel, 1993). The perceived disadvantages of insulin therapy to them (pain, time, strict schedules and eating hours) frequently outweigh the possible benefits on glucose and lipid metabolism. Many are uncertain too about their ability to administer insulin injections.

The current therapeutic strategy in T2DM is still to delay the onset of insulin use and to change from oral agents to insulin at the point in time at which oral therapy becomes ineffective. Yet recent studies suggest alternative strategies may be beneficial. Combinations of insulin and oral agents could provide excellent glucose control with increased weight maintenance, convenience and acceptance to patients. Addition of insulin to oral agents could also be favoured economically, reducing the costs of high dose insulin therapy

Substantial clinical trial data suggests that insulin and sulphonylureas in combination provide an insulin-sparing effect, reducing the total daily insulin dose required to attain glycaemic targets by approximately 30% (Riddle 1996, Johnson 1996, UKPDS57). Adequate control using combination insulin and sulphonylurea therapy can be achieved where single insulin injections fail (VACSDM) and combined therapy is often more convenient for patients moving towards insulin therapy. Reduced weight gain and lower daytime hypoglycaemia risk are reported and are thought to result from more physiological release of insulin during the day in response to sulphonylurea, driven by increases in glucose with meals rather than continuous insulin absorption from subcutaneous depots in patients on daytime insulin injections. Longer-term results especially with regard to lipid changes are not yet available

Randomised clinical trials have shown that combination metformin and insulin therapy can have additive or even synergistic benefit in reducing blood glucose particularly in the fasting state (Golay 1995, Giugliano 1993, Aviles 1998, Jaber 1998). An insulin sparing effect of metformin is reported with a reduction in total daily insulin levels and circulating insulin levels of 25% and a reduction in HbA_{1c} of 1-2%. Favourable effects on weight gain, lipids and blood pressure are documented (Yki-Jarvinen, 1999). Addition of TZD to insulin is equally effective in reducing insulin doses and improving blood glucose control.

Acarbose and insulin in combination appear to produce more modest benefits, reducing postprandial glucose excursions by delaying dietary carbohydrate absorption and reducing weight gain. Reductions in HbA_{1c} (0.4-0.7%), weight, triglycerides and insulin dose have been demonstrated in insulin-treated patients with T2DM randomised to acarbose or placebo (Chiasson 1994, Coniff 1995, Kelly 1998, UKPDS 44 1999).

Intensified insulin therapy results in improved β-cell function and insulin action. Fasting insulin levels increase by approximately 40% with insulin therapy and hyperinsulinaemia may theoretically increase atheroscelerosis risk in patients. This effect is outweighed by the acceleration of diabetic

complications with severe hyperglycaemia, however. Insulin therapy has been shown to improve lipid abnormalities in people with T2DM (DCCT 1995, Scoppola 1995).

3.5: Monitoring Glucose Control

HbA_{1c} determinations with fasting or prandial blood glucose measurements are the recommended measures for monitoring metabolic control in T2DM patients. The power of FPG levels alone to predict metabolic control is poor (Holman 1988, Howey 1989, Wolffenbuttel 1991, Avignon 1997, Bouma 1999). Lack of standardisation of serum fructosamine assays and significant variation in levels with serum albumin, blood collection (venous congestion, patient position), ambulation and diurnal rhythm preclude clinical utilisation of this assay despite its lower cost and potential for automation.

Hyperglycaemia causes glycosylation of tissues, including formation of glycated haemoglobin of which HbA_{1c} is the predominant component. HbA_{1c} accounts for 4-6% of total haemoglobin in non-diabetic individuals and increases with glucose levels. It provides a measure of glucose control over the preceding 2-3 months (Brownlee, 1988) and has been used widely since its introduction in the 1980s. Lack of standardisation and comparison of HbA_{1c} levels across different laboratories can be a source of error.

Early studies of self blood glucose monitoring (SBGM) in the 1970s revealed beneficial effects on glucose control but these findings have not been substantiated in recent research (Allen 1990, Estey 1989, Fontbonne 1989 Gallichan 1994, Miles 1997, Muchmore 1994 Wing 1986) and many have attributed the effects seen to increased education and medical care rather than SBGM itself (Gallichan, 1994). Frequency of glucose monitoring was found to be closely associated with improved glycaemic control in a study of 807 T1DM subjects in Tayside with an HbA_{1c} decrease of 0.7% for every 180 reagent strips dispensed but no such relationship was apparent for 290 T2DM patients in a study by Evans (1999). Glucose monitoring was positively associated with glycaemic control in 562 T2DM patients (Chan, 2000) with reported 0.8% HbA_{1c} reduction in the SBGM group but a recent meta-analysis by Coster (2000) did not provide evidence for its clinical effectiveness. Further research is clearly required and indeed a RCT of systematic self-monitoring in T2DM patients is currently underway in Oxford (DIGEM).

3.6: Fasting and postprandial glucose control

Postprandial hyperglycaemia is the earliest glycaemic abnormality in diabetes and may drive many of the pathophysiological mechanisms of the disease and its complications. It occurs secondary to loss of first-phase insulin secretion and insulin resistance and is associated with hyperinsulinaemia which may relate to increased CVS risk. Prandial glucose is closely correlated with fasting glucose values and high basal FPG levels are associated with exaggerated postprandial glycaemic response. Whilst fasting glucose has long been regarded as the principal predictor of HbA_{1c} the contribution of prandial glucose excursions are increasingly recognised (del Prato, 1999).

It has been suggested that postprandial hyperglycaemia may have better sensitivity, specificity and predictive value of HbA_{1c} than fasting glucose and greater HbA_{1c} reductions with prandial glucose control (Avignon 1997), increased correlation with microangiopathy (DCCT, EDIC 99, NHANES), macroangiopathy (Chicago Heart, Donahue 1987, Barrett-Connor 1997, Hanefield 1999-2000) and premature mortality (Shaw DECODE, 1999) are reported. Increased postprandial excursions occur with diabetes progression and recent data suggests that complications may occur at prandial values well below 11.1mmol early in the course of T2DM. Postprandial hyperglycaemia is associated with postprandial dyslipidaemia, higher blood pressures and prothrombotic states and may mediate macrovascular risk via the metabolic syndrome. Prandial hyperglycaemia contributes significantly to glycaemic instability and poor outcome in gestational diabetes (DeVeciana, 1998).

The Honolulu Heart Study (Abbott, 1987) showed that the risk of fatal and total CHD increased significantly with increasing postprandial glucose values and in the Whitehall study CHD mortality was double in British men with plasma glucose levels of higher than 96mg/dL 2-hours after a meal. The prevalence of all CHD in the Islington Diabetes Survey increased from 9% in subjects with 2-hour PPG <120mg/dL to 20% in subjects with PPG >180mg/dL.

The Diabetes Intervention Study (DIS), an 11-year follow-up of 1000 German patients with newly diagnosed type 2 diabetes mellitus found postprandial glucose but not fasting glucose to be a risk factor for CHD (Hanefield, 2000). This study reported an extremely high incidence of MI compared to nondiabetic controls in another study, the Monitoring of Trends of Cardiovascular Diseases and their Determinants (MONICA) which was conducted over the same period where MI risk related to the degree of control of PPG together with triglyceride and blood pressure levels.

Other studies have reported a causal association between CVD and postprandial hyperglycaemia. Perhaps the strongest relationship between prandial glucose and CVD was found in the DECODE

studies (Qiao 2001, DECODE 1999) in which over 22,000 men and women aged 30-89 years with a median follow-up of 9 years were analysed. The 2-hour blood glucose value was found to be a better predictor of deaths from all causes and CVD than FBG with hazard ratios for fasting blood glucose versus 2-hour blood glucose of 1.21 vs 1.73 for all causes and 1.2 vs 1.4, for CHD.

Postmeal hyperinsulinaemia was also associated with increased CHD risk in the Helsinki Policeman study (Pyorala, 1985), Paris prospective study (Fontbonne, 1989) and Quebec Cardiovascular study (Despres, 1990).

Pharmaceutical agents (meglitinides, α-glucosidase inhibitors, monomeric insulin) with increased action on prandial hyperglycaemia are now available and some studies have demonstrated a greater reduction in HbA_{1c} with therapies directed at lowering prandial glucose than with those lowering FBG (Bastyr, 2000). A consensus conference on prandial glucose was held by the ADA in 2000.

3.7: Potential adverse effects of glucose control

Several potential limitations of intensive glucose control exist including hypoglycaemia, bodyweight gain, hyperinsulinaemia, adverse effects of rapid glycaemic improvement, increased self-monitoring and decreased patient quality-of-life and detailed evaluation of these factors will be undertaken in my study.

The DCCT and DIS studies reported 0.62 and 1.10 severe hypoglycaemia reactions per patient year in intensively treated T1DM subjects and a 3-fold higher risk of hypoglycaemia with intensive compared to standard therapy. Much lower rates were reported in T2DM patients in UKPDS (11% with chlorpropramide, 17.7% glibenclamide, 36.5% insulin compared to 1.2% with diet alone) and severe hypoglycaemia was uncommon (0.4% for chlorpropramide, 0.6% glibenclamide, 2.3% insulin and 0.1% for diet). Low rates of hypoglycaemia were seen in the VACSDM (5 events in the intensive group vs 2 in the standard group, 0.03 vs 0.01 episodes/patient/ year, $p>0.05$) and no major episodes requiring hospitalisation or assistance from others occurred in the Kumamoto study. No correlation between hypoglycaemia episodes and new CVS events were documented in either study and no hypoglycaemic unawareness sequelae were reported. No severe hypoglycaemia and a low incidence of mild self-treated reactions were reported in the intensive insulin trial of T2DM. (Henry, 1998)

Numerous studies have demonstrated weight gain with intensive glycaemic control or exogenous insulin use in type 2 diabetic subjects. A 14% higher prevalence of obesity (BMI >27.8 kg/m^2 men

and >27.3 kg/m^2 for women) was reported in the DCCT intensive therapy group compared to the standard cohort. Weight gain was also significantly higher in the UKPDS intensive therapy group (mean 2.9kg $p<0.001$) particularly in those patients receiving insulin (4kg). Average increases in pretreatment body weight of between 3-9% with exogenous insulin use are reported in the literature and indeed Henry detected an average weight gain of 9.3% after just 6 months of insulin therapy in 1993. No difference in weight gain was seen with intensive therapy in the VACSDM nor the Kumamoto study (mean increase 1.6kg/m^2 with intensive therapy versus 0.8kg/m^2 with standard therapy) and metformin was associated with significantly less weight gain than either insulin or sulphonylureas in overweight UKPDS patients.

Recent DCCT analyses reveal greater increase in insulin dose, total cholesterol, LDL, apolipoprotein levels and systolic blood pressure in patients with the greatest body weight gain and the potential increase in atherogenicity with increased body weight remains a concern. Body weight gain has been found to result in favourable lipid profiles when associated with improved glycaemic control but adverse effects in the absence of glycaemic improvement (Williams, 1999)

Deterioration of pre-existing retinopathy and proteinuria have been reported with intensive glucose control. VACSDM found no significant retinopathy deterioration after 2 years of intensive therapy and demonstrated reduced microalbuminuria progression. A higher reduction of creatinine clearance was, however, seen compared to the conventional treatment arm and correlation of combined new CVS events with low attained HbA_{1c} levels occurred. Proposed mechanisms for the adverse consequences of rapid glycaemic improvement include a role of insulin-like growth factor (IGF) 1 in aggravation of retinopathy and destabilisation of glycated products in the vascular plaques by glucose lowering in microangiopathy.

Chapter 4: Primary Care

4.1: Current role of primary care in T2DM management

The role of primary care in T2DM management has increased substantially over recent years. Primary care teams now provide routine care for >75% of T2DM patients, 20% of district-nurse case-loads relate to diabetes and 12-52% of patients receive shared or hospital care. Diabetes services in primary care are funded through the Chronic Disease Management Programme and the recent development of PCG and PCT structures has provided increased opportunities for monitoring and planning of local services. 20% of PCGs have identified diabetes as a priority area for clinical governance with systems of audit, record-keeping, education and patient care, and 68% have special diabetes interest (Pierce 2002, Williams 2002). Primary care involvement is likely to increase further with the diabetes NSF publication and the potential new GMS contract framework for general practice.

4.2: Current standards in T2DM primary care

Despite this increased role, current standards of T2DM management in primary care remain patchy with considerable variation in both quality and service delivery. The optimal model of T2DM care is not defined but research suggests that standards in primary care are comparable to secondary care where registration, recall and review systems are well organised and practitioners have a special interest in diabetes. Unstructured community care, however is associated with poorer follow up, worse glycaemic control and greater mortality than hospital care (Griffin, 1997).

Despite this knowledge one third of practice diabetes clinics are still run by practices nurses alone, 12% of whom have not attended diabetes training courses in the last three years. Less than one third of clinics have access to a dietitian or podiatrist, 41% lack hospital diabetes referral guidelines and only 19% use hospital or district-wide diabetes management guidelines. Only 57% have estimates of numbers of people with diabetes or a local register (Williams, 2002).

Significant gaps in patient knowledge and self-care occur as a result. These were most recently outlined by the 2002 Audit Commission Survey in which 67% of T2DM patients reported receiving no educational support within the last 12 months and 40% no dietary advice. 25% of respondents understood very little about the effects of illness and diabetes, 20% did not know what to expect if their blood glucose dropped too low and 45% were unaware of their most recent HbA_{1c} result. 20%

of patients did not know how to access out of hours support or advice for their diabetes and indeed such systems were absent in many healthcare trusts.

Outcomes for T2DM in primary care are also substandard. Overall prevalence of glycaemic control still falls short of recommended goals with reported mean HbA_{1c} values of 8.5 to 10% (Hayward 1997, Peters 1998, Bo 1999). Approximately 40-50% patients have poor glycaemic control despite recommended lifestyle modification and oral agents (Valle, 1999), 65% receive annual fundoscopy, 43% urinalysis, 70% podiatry, 84% blood pressure and 83% HbA_{1c} checks. 50% are referred late for specialist foot care (Audit Commission Report, 2000).

4.3: Delivery of Type 2 Diabetes Care in General Practice

The potential for primary care delivery of T2DM services has been explored by Griffin (1998), Olivarius (2001) and Renders (2001). Six studies (Hayes 1984, Porter 1982, Hurwitz 1993, DICE, Hoskins 1993) randomising T2DM patients to hospital, general practice or shared care schemes for review and surveillance of complications were included in the systematic review and meta-analysis by Griffin (1998). Outcome measures for the 1058 patients included process (general practice follow-up appointments and reviews, hospital consultations and admissions), morbidity (symptoms, weight, blood pressure, glucose control), patient satisfaction, diabetes knowledge and mortality measures. No difference in mortality between patients randomised to shared care or hospital follow-up were located. Those randomised to primary care had lower HbA_{1c} values (weighted difference in means of -0.28%, 95% confidence interval -0.59 to 0.03) and losses to follow-up were found to be significantly less with prompted GP care (OR 0.37, 95% confidence interval 0.22 -0.61). Patients randomised to primary care with less well developed support had worse outcomes however than those receiving hospital follow-up.

A six-year randomised controlled trial conducted by Olivarius in 474 Danish general practices in 2001 reported significantly lower plasma glucose levels, HbA_{1c} and systolic blood pressure in an intervention group with regular follow-up, individual goal-setting, prompting of doctors, clinical guideline use, feedback and continuing medical education than a comparison arm. Median plasma glucose levels were 7.9mmol/L in the intervention group compared to 8.7mmol/L in the comparison group, median HbA_{1c} was 8.5% versus 9.0% and SBP 145mmHg versus 150mmHg respectively. Doctors in the intervention group referred few patients to hospital diabetes clinics, arranged more follow-up consultations and set more optimistic goals.

Renders (2001), reviewed 48 publications evaluating the effectiveness of interventions directed at healthcare professionals caring for diabetes patients in primary care, outpatient or community settings. A small beneficial effect in glucose control was seen in studies in which nurses (Day 1992) or pharmacists (Jaber 1996) assumed part of the physician role. Process outcomes were improved with organisational interventions including structured review and complex professional interventions (Peters 1998, Hurwitz 1993) but effects of these interventions on health-related outcomes was less clear and poorly assessed. Nurse involvement and patient education were associated with positive patient outcomes. The review concluded that combinations of professional and organisational interventions, nurse involvement and patient education do impact positively on the process and outcome of care (Weinberger 1995, O'Connor 1996, Aubert 1998). Methodological limitations of the twenty seven RCT, twelve 'before and after' studies and two interrupted time series studies in the review were described. Adequate methods for the concealment of allocation were present in only six RCTs and contamination of the comparison groups was likely in 15 studies with randomisation within practices. Poor comparability between intervention and comparison groups, lack of adequate blinding in assessing outcomes, short follow-up, lack of a priori statistical power calculations and failure to include ITT analyses were also criticised.

4.4: Diabetes intervention studies in primary care

Meta-analyses of primary care diabetes intervention studies conclude that educational programs can confer a broad range of patient benefit with larger effect sizes often seen for self-reported measures including knowledge, diet and exercise than objective outcomes such as skills, weight change and glucose control. Brown (1990) and Roter (1998) revealed effect sizes for educational interventions on HbA_{1c} of 0.41 and 0.56 respectively but the short term nature of such effects was highlighted by Padgett (1988), who demonstrated a decrease in effect size from 0.36 six months after education to 0.03 at one year. Effects for compliance indicators including pill counts, pharmacy record reviews and knowledge were strong in these studies but only psychological and knowledge were moderately maintained with time. Interventions based on ideas of informed choice, self-management skills, group work or behavioural/social learning approaches were more effective than narrow didactic approaches.

Other factors contributing to diabetes self-management include beliefs and personal models of disease, motivation and socio-environmental factors (Glasgow, 1999). Gender, education, income, intelligence, health knowledge, personality type and sociodemographic variables do not consistently predict adherence to medical regimenss (DiMatteo 1982, Griffin 1998). Cognitive strategies using techniques to test and strengthen motivation to act and behavioural strategies supporting the

implementation of chosen strategies and build them into habits appear successful. The nature of the patient-practitioner relationship in which the education is applied is also important (Stewart, 1996).

Many studies have examined the relationship between communication and health outcomes in diabetes. Stewarts review (1996) of analytical studies and RCTs of doctor-patient communication and health outcomes concluded that both the nature and process of communication in consultations influenced patient outcomes such as glucose control, blood pressure, symptom resolution, functional status and emotional distress. Positive outcomes were associated with the patient asking questions, agreeing about the nature of the problem and perceiving that a full discussion had taken place, practitioners answering questions with clear information, eliciting patients ideas concerns and expectations and showing empathy.

Participatory communication consultation styles with patient-centred interviewing skills, data gathering with open sensitive questions, relationship building with emotional support, reassurance, empathy and personal regard, and partnership skills using prompts, signals of interest, listening skills, interpretation and paraphrasing have been associated with improvements in metabolic control in diabetic patients compared to controlling communication styles (Street, 1993) but the causal pathways remain unclear.

Effects of patient activation and empowerment have been investigated in randomised controlled trials by Greenfield (1988), Rost (1991), Anderson (1995), Pill (1998) and Kinmonth (1998). Techniques to promote proactivity and shared decision-making included provision of patient guides to help identify, phrase and rehearse questions, concerns and issues for the visit, teaching of communication skills to enhance patient involvement in doctor-patient interactions and more complex empowerment interventions to promote independent patient competence in decision making and self-management. Outcomes for these studies included $HbA_{1c,}$ functional status and or quality of life indices.

Activated patients in the Greenfield study, in which a twenty-minute intervention was used to improve information seeking skills, facilitate patient involvement by exploring medical decisions that were likely to arise in the upcoming visit and provide skills to enhance participation, had lower HbA_{1c} levels and fewer physical limitations but no change in satisfaction or diabetes knowledge. HbA_{1c} was significantly correlated with the number of conversational acts, controlling acts and degree of effective information elicitation in this study. No significant effect of patient activation on HbA_{1c} was found in a subsequent hospital trial by Rost.

Most empowerment studies have equated increased patient-centredness to improved metabolic control, self-reported health and functional status. Langewitz (1997) provided patients with detailed

knowledge about insulin requirements in relation to different glucose challenges enabling them to take informed control of their insulin regimen. HbA_{1c} was significantly improved at four months despite a low baseline value of 6.6% but was not significantly changed at one year. Improvements in the doctor-patient relationship, satisfaction, anxiety, depression and hypoglycaemia were reported. The Anderson self-efficacy program emphasised biomedical, psychological and social aspects of coping in diabetes management. 46 patients were randomised to program attendance or waiting list control. HbA_{1c} was significantly improved at 12 weeks along with self-efficacy. Pill devised an intervention for general practitioners and nurses in a UK general practice study of 190 patients with established T2DM in 1998. Patients were encouraged to air personal concerns about their disease, choose self-care areas for discussion and set personal goals using the readiness to change behavioural model. The intervention was poorly applied and had no effect on HbA_{1c} or other measures of health status, wellbeing or satisfaction. HbA_{1c} was also not significantly improved in the UK general practice randomised clinical trial of 360 newly diagnosed T2DM patients by Kinmonth. A patient-centred approach using a booklet to enhance patient questioning and agenda-setting prior to the consultation and nurse skills training to elicit patient agendas, negotiate behaviour change and support individual choices with the stages of change model was used. Greater treatment satisfaction and wellbeing were reported by patients attending trained practitioners but knowledge scores, triglyceride and BMI were significantly worse in the intervention group.

4.5: Glucose optimisation studies in primary care

Most studies of glucose optimisation in T2DM are hospital-based with populations comprising selective populations of hospital patients and specialist management techniques. Few have examined the feasibility of attaining strict glycaemic control in general practices. Primary care studies have traditionally focussed on structural and organisational issues involved in delivery of care, variations in care between practices and comparison with hospital care. Systematic attempts to improve blood glucose control in general practice with earlier use of OHA combinations and insulin, reporting both outcomes and adverse events are rare.

De Sonnaville (1998) used protocolized glucose lowering therapy advice, home glucose monitoring and insulin in his 2-year prospective controlled cohort study of structured care in general practice in 22 study and 6 control practices, and described similar results in a larger sample of 350 T2DM with greater mean age (65.3yrs) and T2DM duration (5.9 yrs). Mean HbA_{1c} decreased from 7.4% to 7.0% in these patients with 54.3% achieving targets <7.0% and increased from 7.4 to 7.6% in 68 comparable controls with 44.1% achieving targets. Insulin was used in 30% of study practices and 9% of controls with a low reported risk of severe hypoglycaemia (0.019/pt year). Wellbeing was

unchanged during intensified therapy and satisfaction with therapy tended to improve as seen in our study. Management with insulin however, was experienced as more demanding and high insulin doses were associated with low mood.

Other studies have suggested that normoglycaemia maintenance is difficult in primary care settings, and that insulin use is rarely effective in achieving tight glycaemic control (Hayward, 1997). The complex regimes required to maintain adequate glucose control have been criticised. Diminished quality of life, increased hypoglycaemia, weight gain and unacceptable perceived treatment burden are cited as the most likely reasons for difficulties.

4.6: Insulin initiation in primary care

Insulin use is still often considered a last resort in T2DM management in general practice to be used when uncontrolled hyperglycaemia occurs with maximal OHA therapy. Most practices do not have facilities or trained staff to initiate and manage insulin and consultation lengths are not conducive to the counselling and education required for its use. Most studies investigating insulin are hospital-based but the findings below are relevant to general practice use.

Usual barriers to insulin include hypoglycaemia, weight gain and potential atherogenicity together with needle phobia, diet restriction, economic considerations and employment issues in patients. Severe hypoglycaemia is rare in the absence of CVS or renal disease but symptomatic biochemical episodes are common. Hypoglycaemia risk is affected by the regime selected and can be reduced substantially with newer agents. The association between atherogenicity and insulin use remains unclear but the UKPDS demonstrated no increased CVD mortality or morbidity with insulin use. Weight gain in the region of 2.5-7.5kg is reported with insulin therapy during the first year with the rate subsequently diminishing with time. The mean weight gain after fifteen years of use in UKPDS was approximately 7 kg yet only a small, non-significant increase in BMI after eight years was seen with insulin in the Kumamoto study.

The benefits of insulin, its established safety profile and ability to maintain long-term glycaemic control without polypharmacy use are not shared by other therapies and are often overlooked. Its ability to restore normal insulin sensitivity, improve lipid profiles and increase wellbeing are also significant (Johansen 1999). Newer insulin products can provide more flexibility for patients with unpredictable lifestyles than oral agents and are highly effective in controlling postprandial glucose excursions. Insulin is advantageous too where contraindications to oral agents exist or tolerability is low. Insulin use was beneficial in T2DM patients with acute MI and combinations of insulin with

metformin therapy have been found to be advantageous reducing hypoglycaemia (Yki-Jarvinen 1999) and weight gain more than insulin use alone. An insulin sparing effect of 15-32% is also reported. A meta-analysis of sulphonylurea plus insulin use reported better glycaemic control (1.1% HbA_{1c} reduction with combination compared to 0.25% with monotherapy), reduced daily insulin dose and no adverse effect on body weight.

4.7: Study Rationale

We are unaware of other studies that have systematically applied a protocol-driven, treat-to-target approach to glucose control, with earlier use of OHA combinations and insulin to target basal and prandial glucose and achieve normoglycaemia in a primary care setting.

Whilst Gaede demonstrated clearly the benefits of a target-driven, long-term, intensified intervention aimed at multiple risk factors in hospital patients with T2DM and microalbuminuria, reducing CVS risk and microvascular events by 50%, and other authors (Riddle 2000, Skyler 1996, Holman 1988) have evaluated algorithm use and titration rules to adjust therapy doses in T2DM populations no such evaluation of primary care interventions have been trialled. Involving T2DM patients in CVS risk monitoring and informing them of their own versus target levels of risk factors is known to improve attainment of targets and reduce progression to vascular complications (Rachmani, 2002) and the provision of a multifaceted intervention with individualised patient goals, education and surveillance significantly reduced risk FPG, HbA_{1c} and risk factor levels in 874 Danish T2DM patients (Olivarius, 2000). The value of integral education in structured T2DM programmes was demonstrated clearly by Van der Arend (2000) and the benefits of protocol-driven management with flowcharts was demonstrated by Goudswaard (2003) in 52 Dutch practices, reducing HbA_{1c} from 8.9% to 6.7% over fourteen weeks.

The literature review provided in Chapters 2-4 highlights clearly the degree to which blood glucose management in T2DM remains substandard, the persisting emphasis on monotherapy, gradual dose titration and delayed insulin use and the need for polypharmacy and multiple risk factor intervention to reduce morbidity and mortality in T2DM patients. The optimal choice of therapies and potential advantages of using OHA combinations to specifically target both basal and prandial components of the glucose curve in T2DM patients have not been fully elucidated, and systems to enable insulin initiation in routine general practices not clearly established. This DPhil study was designed to address these issues and build on current knowledge in the field. A nurse-led, protocol-driven, treat-to-target approach with provision of integral education was selected to enhance applicability to the general practice setting.

4.8: Study Objectives

The principal objectives of this D Phil study were:

A. To develop a protocol-driven, treat-to-target approach to glucose control with earlier use of OHA combinations and insulin, and CVS risk factor modification in general practice T2DM.

B. To provide training, resource and educational materials to enable earlier use of OHA combinations and insulin initiation to be accomplished by general practice nurses.

C. To evaluate the feasibility of using this approach in general practices with respect to:

- Practice and patient participation
- Reasons for non-participation and characteristics of non-respondents
- Number of therapies needed to attain normoglycaemia
- Number of patients requiring insulin therapy and ease of initiation in general practices
- Patient satisfaction and health perception with earlier use of OHA combinations and insulin
- Patient adherence to increased therapies, glucose monitoring and insulin
- Acceptability to practice staff and patients, and additional support required
- Safety and adverse events in patients

D. To evaluate the efficacy of this approach with respect to:

- Fasting, prandial glucose, HbA_{1c} and hypoglycaemia episodes
- Weight change in T2DM patients
- Cardiovascular risk factor modification

E. To estimate the potential achievable benefits of glucose and cardiovascular (CVS) risk factor modification using this programme compared with standard care over the same period.

F. To apply therapy sequences for a potential UK general practice randomised trial of glucose control in T2DM examining the relative CVS benefits of metformin versus rosiglitazone and estimating their comparative efficacy.

G. To comment on implementation of this approach in practice.

Section Two: Study Design and Methodology

This section describes the design and methodology for the study, and is divided into six sections.

Section 5.1 outlines the randomised and observational elements of the study design whilst section 5.2 details the population and recruitment process. Practice and patient recruitment, inclusion and exclusion criteria are listed in sections 5.2.1-5.2.2 and the procedures involved in patient consent in section 5.2.3. Withdrawal of patients before completion of the study is discussed at the end of this section, and the number and reasons for study withdrawals are provided.

Study interventions are discussed in section 5.3. A description of the randomised algorithms and the protocol-led, target-driven approach is provided in the first two sections, procedures for gating and therapy titration in section 5.3.3 and management of lifestyle and CVS risk factors in section 5.3.4. The final part of this section describes the training provided for practice nurses to enable them to undertake study tasks and initiate insulin therapy. The visits section of the study resource manual is located in Appendix 4.

Section 5.4 examines the outcome measures for the study in terms of biochemical measures, glucose monitoring results and validated questionnaire tools. Delivery, storage, preparation and processing of samples for the DTU biochemistry laboratory and procedures for monitoring of quality assurance are described in section 5.4.1. Selection, properties, calibration and standardised use of glucometers is discussed in section 5.4.2 and the Euroqol, Wellbeing and Diabetes Treatment Satisfaction validated questionnaire scales detailed in 5.4.3.

Section 5.5 lists the statistical techniques employed in the study and summarises the principal tests applied for the recruitment, randomisation, normality testing and analysis of major variables.

Finally section 5.6 outlines the ethical considerations, funding and indemnity arrangements for the study. Design of study documentation, data handling procedures and storage of confidential patient is detailed at the end of this section.

Chapter 5: Study Design and Methodology

5.1: Study design

The study design for this project comprised two elements; the development of the protocol-driven, treat-to-target approach and gating mechanisms for therapy titrations and the application of therapy sequences for a potential trial of glucose optimisation in UK general practice.

A randomised, open-label, parallel-group study design was applied for the latter, in order to gauge relative benefits of metformin versus rosiglitazone use on CVS outcomes. UKPDS showed that metformin was advantageous in overweight diabetic patients, reducing hypoglycaemia, weight gain and macrovascular risk (32% risk reduction, p=0.002) more than sulphonylureas or insulin. The potential benefits of TZDs versus metformin on CVS risk over and above their glucose lowering effect are not fully elucidated and this design enabled early trends to be evaluated before major trials are performed. Pure comparison of the first-line agents was maintained by randomisation to identical second-line therapies avoiding drug crossover and substitution. Placebo use was considered unethical because of the proven beneficial effects of existing therapies but the glipizide arm was used as a control arm. Further details of this design are described in the study intervention section 5.3 and illustrated in figure 5.1.

A central computer randomisation procedure was used to allocate study therapies. Randomisation was performed at an individual level with minimisation criteria to achieve balance across therapy allocations. The minimisation programme was designed using a random sample of sixty UKPDS patients from six UKPDS centres who fulfilled study inclusion criteria. Criteria for minimisation included gender (male versus female), age (<65 years versus ≥65 years), obesity (BMI<30 versus BMI ≥30 Kg/m^2), previous therapy (diet versus OHA) and practice centre. All study therapies were prescribed open-label on FP10 prescriptions. No blinding occurred.

A protocol-driven, treat-to-target approach emphasising earlier combination OHA and insulin use, targeted reduction of both basal and prandial glucose for maximal HbA_{1c} lowering and strict glucose and CVS risk targets was superimposed on this structure. Pre-specified therapy schedules were issued to patients listing the proposed therapy increases that would occur if targets were exceeded and clear guidelines for glucose and CVS risk modification provided for nurses. A dose titration rule was devised based on home glucose monitoring values and was verified using clinic FPG, PPG and

HbA_{1c} values. Therapy additions and dose titrations were separated by monthly intervals to permit examination of the side effects, tolerability and acceptability of individual agents.

Finally an observational comparison study of glucose and CVS risk factor outcomes in patients recruited and not recruited to the study was incorporated.

5.2: Study population

The study population comprised ambulatory patients with established T2DM, aged 40 to 75 years, who had elevated HbA_{1c} levels (>6.4 and <10.0%) on diet or oral monotherapy. Patients with impaired renal function (creatinine >150mmol/L), liver failure (ALT >1.5xULN), pregnancy, malignancy or life-threatening illness, contraindications or hypersensitivity to study medication or who were unable to comply with the protocol were excluded. The latter group included patients who could not understand English, perform home blood glucose monitoring, take insulin or attend practice clinics for assessment.

No apriori specification of sample size was made as the study planned to recruit the maximum number of patients from the centres. The proportion of patients recruited, characteristics of respondents and reasons for non-participation were useful outcomes which helped to assess the generalisability of the programme.

5.2.1: Practice recruitment

Twenty practices with an interest in diabetes were selected from Oxfordshire and Buckinghamshire health authority regions. The study was presented to GP partners, practice nurses and research staff in each centre and practical issues were discussed. Four Oxfordshire and three Buckinghamshire practices were recruited. The recruitment figures are shown in table 6.1.

5.2.2: Patient recruitment

Computerised practice diabetes registers were used to search for T2DM patients, aged 40-75 years with HbA_{1c} levels 6.4-10.0% on diet or oral monotherapy. A study invitation letter printed on practice headed notepaper and signed by the patients' GP was mailed to each eligible subject identified by this search. All patients were subsequently contacted by telephone to assess their interest in the study and to discuss queries. During this call their T2DM duration, current medication, HbA_{1c} level and comorbidity were determined and mobility and eyesight verified to be

sufficient for the demands of the study. All patients were specifically asked whether they were willing to attend their surgery at monthly intervals, increase their diabetes therapies, take twice-weekly seven-point glucose profiles and consider insulin use. The appraisal of diabetes (ADS) questionnaire was used in all patients who provided consent. An eligibility appointment was made for patients who were interested in joining the study and the principal reason for non-interest recorded for all other patients. This information was recorded on a pre-defined spreadsheet in preparation for subsequent statistical analyses. Patients accepting recruitment to the randomised trial were seen at fourteen scheduled visits over the one year timescale of the study and outcomes at one year were compared with those in patients who declined participation.

5.2.3: Patient consent

All patients provided written informed consent for study screening tests and study entry. Consent forms were returned to the DTU centre and a copy maintained in the subject folder.

5.2.4: Study withdrawals

Recruited patients withdrawing from the study before completion were seen on withdrawal and a year from study entry to complete final assessments and biochemical measurements. Those withdrawing from the study because of significant laboratory abnormalities, serious adverse events or concurrent illnesses were followed until resolution of these abnormalities. Where possible those who moved away from the practice area during the study were contacted at closeout to complete final assessments. All patients who declined to participate in the randomised study were followed up at one year.

5.3: Study Interventions

5.3.1: Randomised therapy sequences

All recruited patients were randomised to one of six pharmacologically distinct therapy sequences (labelled A-F) based on three primary therapies, metformin, rosiglitazone and glipizide. Each of these agents was designed to primarily lower basal glucose values and each was continued throughout the study. An agent targeting prandial glucose was added at three months and doses of both titrated upwards at monthly intervals using the dose titration schedules below and home glucose monitoring values aiming for fasting glucose targets of < 6mmol/L and 2-hour prandial targets < 8mmol/L. Where fasting targets were exceeded with maximal oral therapy isophane insulin

was added and where prandial targets were exceeded humalog (lispro insulin) was added. Glucose therapies were prescribed monthly on FP10 prescriptions by general practices. Rosiglitazone, used under DDX licence in the study, was issued to practices directly from the Oxford study centre. Insulin pens were provided courtesy of Lilly and lancets, meter strips and needle disposal devices prescribed on FP10. The randomised therapy sequences are shown in figure 5.1.

5.3.2: Protocol-driven approach

A resource manual and monthly visit schedule specifying all tasks was designed for the protocol-driven, treat-to-target approach and patients received an individual treatment plan outlining their likely therapy progression. Eligibility was verified, screening tests performed and study details discussed at visit one and recruitment consent obtained two weeks later. Healthy lifestyle literature was discussed, food diaries reviewed, glucose monitoring taught and cardiac risk calculated using the Joint British Heart Coronary Risk Prediction Chart. Randomisation was undertaken at two months.

5.3.3: Treat-to-target titration of therapies

OHA doses were titrated at monthly intervals using a gating approach based on the last two weeks of home blood glucose monitoring results recorded by the patient. Whenever 75% or more of the fasting glucose values exceeded targets (<6.0mmol/L) a protocol-driven increase in basal therapy dose was undertaken and whenever 75% or more of prandial glucose values exceeded targets (<8.0mmol/L) a prandial therapy dose increase was recommended. Safety features were included in the algorithm so that if intercurrent illness, frequent hypoglycaemia or adverse events had occurred dose increases were amended. Clinic FPG and HbA_{1c} results were also used to verify therapy progression. Starting insulin doses were commenced using the Holman-Turner sliding scale and increased initially at weekly intervals according to a specified algorithm using the last two weeks of home glucose values.

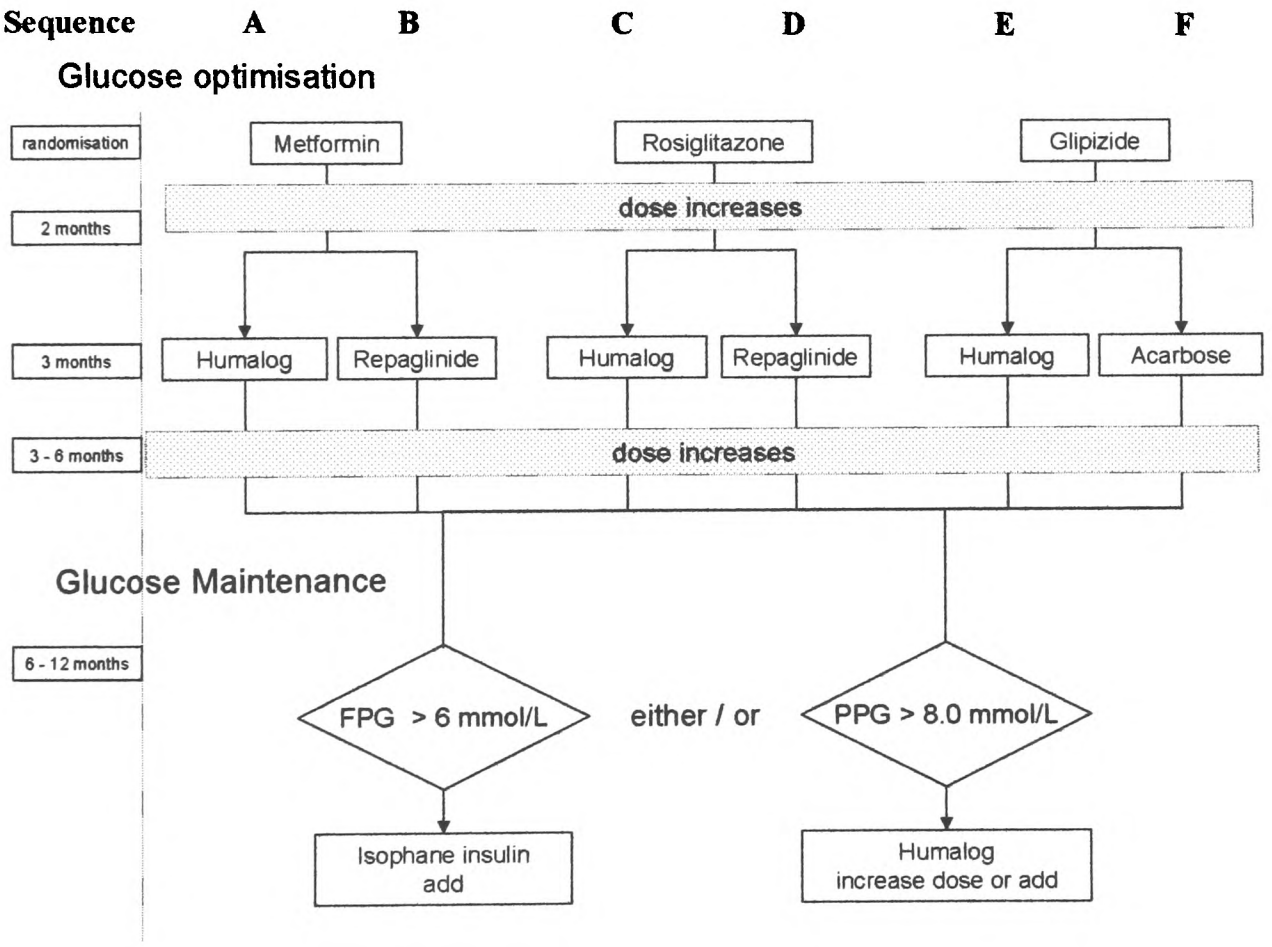
5.3.4: Concomitant medication

Concomitant medication was recorded monthly and potential interactions with study therapy verified prior to use with the supplied drug data sheets. All patients experiencing previous hepatic toxicity with troglitazone or with contraindications or hypersensitivity to study therapies were excluded.

5.3.5: Lifestyle and CVS risk factor modification

CVS risk factor modification was emphasised throughout this trial by provision of standardised guidelines, clear targets and prompted measurement of risk factors on CRFs at visits. Titration of medication for blood pressure and lipid measurements was not however prompted or verified. All patients received lifestyle advice at baseline and a food diary was used to provide feedback on potential diet improvements. Blood pressure was monitored at each visit and BHS guidelines issued to nurses. A full lipid profile was measured at the beginning and end of the study. Cardiac risk was calculated at baseline and one year using the Joint Heart Guidance and novel biochemical CVD risk factors at baseline and one year. Results were discussed with patients and educational leaflets given.

Figure 5.1 : Randomised Therapy Sequences



5.3.5: Training of practice nurses

A training day was organised for all practice nurses to provide an overview of the design, objectives and operation of the study. Clinical and practical components of patient care at study visits were discussed, standardised measures for procedures outlined and queries resolved. Essential skills including insulin training, home blood glucose monitoring and meter downloads were demonstrated and teaching scenarios rehearsed using roleplay. Detailed discussion of therapy algorithms, dose

adjustments, insulin use, data collection, biochemical, clinical, practical and safety issues was included. Nurses were seen individually prior to study onset to practice these skills further and to resolve any difficulties. A questionnaire was provided for each nurse to provide feedback about this training programme.

Educational materials to enable insulin initiation and adjustment in primary care were developed and tested. A checklist was provided for practice nurses to ensure that detailed information on the rationale for insulin use, action and duration, pen devices, injection techniques, insulin storage, sharps disposal, hypoglycaemia, DVLA implications, effects of illness, exercise, eating out and alcohol was provided to all patients. Insulin initiation was observed frequently and patients were seen weekly for one month after insulin addition to ensure transfer of skills. 24-hour telephone cover was provided in case of problems, hypoglycaemia or serious adverse events. All patients received an insulin treatment identity card. Broader insulin training was provided at a two-day hospital workshop. Nursing staff without previous clinical diabetes experience attended a diabetes course within Oxford.

A programme of patient education using DUK literature and study specific information was designed to run alongside the study. An initial information sheet was mailed to patients outlining the study background and objectives of the study; the therapies involved, likely side effects and need for regular clinic attendance and increased therapy use. Dietary guidance, exercise advice, healthy living and smoking cessation leaflets were designed exclusively for the study and teaching plans for practice nurses devised.

5.4: Outcome measures

The major outcomes of the study were the feasibility of operating a nurse-led, protocol-driven, treat-to-target approach in primary care and the efficacy of this approach in terms of the degree of glucose and CVS risk factor modification attained.

Feasibility was assessed with respect to participation of practices and patients and the acceptability of therapy algorithms in terms of safety, adverse events, QoL, health perception, adherence and therapy satisfaction in patients. Efficacy was assessed in terms of the degree of FPG, PPG and HbA_{1c} reduction attained, the proportion of patients achieving normoglycaemia, the number of therapies required together with the degree of weight, biochemical CVD markers and risk factor modification in patients compared to standard care.

Secondary outcomes included the feasibility and relative benefit of using the specific therapy algorithms for a large RCT of glucose reduction and CVS outcomes in UK general practice.

5.4.1: Biochemical determinations

Glucose measurements (FBG and HbA_{1c}) were made monthly whilst markers of microvascular disease risk (creatinine, urinary albumin) and macrovascular risk (hsCRP, lipoprotein A, lipids, homocysteine and D-dimer) were measured annually. Safety checks (monthly ALT and six monthly FBC) were undertaken in patients on rosiglitazone therapy.

Samples were delivered to the Radcliffe Infirmary by courier systems or study personnel. No special storage or delivery conditions were adopted within the study centres. All samples were centrifuged and pippetted at the DTU by myself with the help of research nurses and were delivered to the DTU central biochemistry laboratory for analysis. Assays were monitored at the DTU by a computerised quality assurance programme, 'QSTAT', using tri-level quality control sera with application of Westgard rules for acceptance of results. National external quality assurance schemes were used if available.

HbA_{1c} was measured in EDTA whole blood by high performance liquid chromatography (Variant^{TM} Hb Testing System, Biorad Laboratories Ltd, Hemel Hempstead, UK) and plasma glucose was measured in plasma (fluoride/oxalate) by the hexokinase method for the Beckman Synchron CX4 Delta analyser. Lipids and lipoproteins were measured in EDTA plasma using the Beckman Synchron CX4 Delta analyser (Beckman Instruments Ltd, High Wycombe, Bucks, UK) using no correction for free glycerol (approximately 0.11 mmol/l) for triglyceride measurements. Intra-assay variation (CV) for the mid control were 2% for triglyceride 1.4 mmol/l, 1% for cholesterol 5.5 mmol/l, 1.6% for LDL cholesterol 3.9 mmol/l, 2% for HDL cholesterol 1.31 mmol/l, <2% for HbA_{1c} and 2% for glucose. Alanine aminotransferase (ALT) was measured using the Beckman Synchron CX4 Delta System and enzymatic rate method based on the ECCLS standard. Creatinine was assayed using the modified rate Jaffe method and full blood count using the Bayer H1 Haematology system. Finally urine albumin was determined by an immunoturbidimetric method using goat anti-human albumin antiserum (Incstar Ltd, Winnersh, Berks, UK) and human serum protein calibrator (Dakopatts, High Wycombe, Bucks, UK).

5.4.2: Glucose monitoring measurements

Blood glucose meters were compared to determine the ideal machine for study use and the precision QID meter selected. This system is the standard meter recommended by OCDEM and is the most widely used meter in Oxford practices. It is simple to operate, pre-calibrated, requires only 3.5μL of blood, produces results in 20 seconds and has software to enable downloading of glucose results to a central computer. Utilising non-wipe biosensor technology for glucose measurement, sensor electrodes are foil wrapped to minimise deterioration in storage and are available on FP10. The meter uses whole blood samples but is referenced to lab-like results. A correlation of 0.99 between Precision QID results and the YSI2300 and hexokinase glucose method is reported with CVs <5% and correlation coefficient of 0.99 with capillary, venous and arterial blood. Noticeable variation in the magnitude of bias at different concentration levels occurs with variation from 8% to –3% with capillary blood. Haematocrit appears to have a significant effect on the level of the bias encountered (=-0.72, $p<0.001$).

Patients received detailed training in HBGM and 2-hour prandial glucose measurement at the onset of the study. A timer was provided to assist patients with these measurements. Twice weekly 7-point glucose profiles were collected by patients and used for therapy adjustment. Glucometer results were regularly downloaded to a central computer. A standard operating procedure (SOP) for use and calibration of the Precision QID meter using the G2 test solution was provided for all practice nurses and performed quarterly.

5.4.3: Questionnaire measurement instruments

Validated quality of life questionnaires were issued to patients at monthly intervals throughout the study to evaluate the effects of glucose optimisation, increased therapies and insulin use. The scales used were the EQ5 health thermometer (Euroqol Group 2001), the DTSQ (Bradley 1994) and the WBQ-12 (Lewis 1990). The ADS scale (Carey 1991) was administered to patients at study onset to gauge the perceptions of recruited and non-patients towards their diabetes.

The Appraisal of Diabetes Scale (ADS)

The ADS, a 7-item measure with Likert-type scales, designed by Carey to assess adult patients' appraisal of their diabetes, was used to compare characteristics of recruited and non-recruited patients at baseline. Items address degree of upset caused by diabetes, perceived amount of control over diabetes, degree of uncertainty, perceived vulnerability to worsening of diabetes, personal

control over diabetes, self-efficacy in coping with diabetes and effect of diabetes on life goals. The scale is a useful screening instrument to measure adjustment to diabetes. It is easily read to patients, takes less than five minutes to complete and is very acceptable to patients as it enquires only about diabetes unlike most traditional psychological scales.

This scale was developed on the basis of research by Lazarus, Folkman, Gong-Guy and Hammen with several items adapted from Hammen/Mayol's Attribution Questionnaire and customised for the diabetes context. Its reliability and validity was assessed in two-hundred adult male outpatients at the Syracuse Veterans Administration Medical Centre Diabetes clinic (mean age 58.4 years) and the scale was shown to provide an internally consistent dimension of diabetes appraisal with acceptable item-remainder correlations, a Chronbach's coefficient α of 0.73 and a single component eigenvalue of 2.73. Stability with repeated administration was shown and validity supported by correlational analyses with several related self-report measures. Scores have been found to predict glycaemic control and diabetes-related quality of life.

The Wellbeing (WBQ-12) Questionnaire

The wellbeing questionnaire was designed in 1982 to provide a measure of depressed mood, anxiety and positive well-being for a WHO study evaluating new diabetes therapies and intensified regimens. Unlike most non-specific depression scales, it is designed to be most sensitive to cognitive depression symptoms with minimal inclusion of the somatic symptoms (eg weight loss) which are common in poorly controlled diabetes and could confound evaluation of mood states. Several items address energy/tiredness but these are not included in the depression subscale. The wellbeing questionnaire is also advantageous over the other non-specific depression scales (eg HAD scale) as it captures positive effects of therapy change and improvements in diabetes management.

The Wellbeing scales were originally used in adults with insulin-treated diabetes but more recently have been used in studies evaluating the effects of new treatments and in patients transferring from tablet to insulin therapy. The effects of educational interventions in tablet-treated T2DM patients have also been studied and scores from the sheet are now included in the multicentre European Diabcare project and endorsed by the WHO.

The 12-item questionnaire is a shortened one-page version of the scale and was developed for use in an RCP national audit of diabetes care. The four subscales are maintained (depression, anxiety, energy and positive well-being) but the tool has slightly less sensitivity than the full scale. Its simplicity and ease of completion for patients has promoted its use in many subsequent studies.

The Diabetes Treatment Satisfaction Questionnaire

The DTSQ is a useful tool which focuses on patients' satisfaction with the outcome of medical care. It measures satisfaction towards therapy including items relating to perceived frequency of hyperglycaemia and hypoglycaemia and has been used previously in studies evaluating treatment for improved glucose control (Jennings 1991).

The scale was designed for use initially in the Sheffield feasibility study of CSII pumps (Lewis 1988) and was subsequently modified by Bradley to measure absolute satisfaction in the WHO Multicentre European Study of CSII pump treatment versus intensified injection therapy, and for use in tablet treated patients in subsequent general practice studies. The current scale produces a single measure of satisfaction from summed scores for questions 1,4,5,6,7,8 ranging from 0 (very dissatisfied) to 36 (very satisfied) and produces the greatest discriminatory power. Single items have also proved to be sensitive to change despite their limited range of scores (0 to 6).

The DTSQ has been widely used in a general practice setting and has proved to be highly reliable with good construct validity, sensitivity to change and discriminatory power on testing.

5.5: Statistical analyses

Recruitment and randomisation were analysed using the consort approach. Practice demographic data was obtained to compare patient characteristics in different centres and factors influencing participation were determined. The demographic variables of recruited and non-recruited patients were tested for normality using frequency plots and the nscore test, and the randomisation process checked to ensure a balanced distribution of patients between therapy groups. The number of patients who completed the study was verified and the reasons for withdrawal documented.

Demographic characteristics of recruited and non-recruited patients and therapy groups were compared using frequency counts and chi-squared analyses for categorical data, medians/IQR and Mann Whitney U tests for continuous non-normal data and means/SD and ANOVA analyses for continuous normal data.

The proportion of patients attaining target FPG, PPG and HbA_{1c} values were analysed for the three primary therapy groups. Intention to treat analyses (ie for the entire subset of recruited patients) are provided for all cases and provide the most valid statistical analysis. Cohort or valid case data (ie for the subset of completing patients) is provided to determine potential differences between patients

who withdrew from the study and the entire group of patients. Finally use of cross-sectional data is reserved for situations where ITT analyses were difficult (ie with PPG where non-study participants did not monitor prandial glucose). This is also shown in occasional figures to display the actual monthly trends in the variable within protocol-adherent patients.

The mean change in variables with time from randomisation was determined and ANOVA analyses used to compare reductions with different therapy arms. ANCOVA analyses were also performed to determine the differential effects of therapies taking into account their baseline differences. AUC and IAUC analyses were used wherever repeated measures analysis was undertaken and provide the most valid statistical interpretation. Where data within the study was non-normally distributed but was known to be normally distributed in larger-scale studies eg UKPDS both parametric and non-parametric tests were included. Frequency and severity of hypoglycaemia episodes was compared across treatment groups.

The number of therapies used and distribution of drug doses was examined and survival analysis techniques were used to compare the time to basal insulin requirement in different therapy groups. The proportion of patients requiring humalog or isophane within each algorithm was determined. All between therapy comparisons were performed on a serial cohort and ITT basis.

Food diary entries at baseline were examined to evaluate the dietary habits of patients in the study. The effect of therapies on weight, BP and lipids was analysed using ANOVA analyses and the number of patients achieving standardised BMI, BP and lipid targets was examined. Cardiac risk at baseline and 1-year was compared for all patients with the Joint Heart guidelines and surrogate biochemical markers of cardiovascular risk were compared across therapy groups at baseline and one year. Change in CVS risk factors over the year were examined with paired t tests.

Patient adherence to lifestyle advice, therapy and glucose monitoring was an important component of this study and subjective reports of adherence were documented monthly. Questionnaire results for diet, lifestyle and therapy adherence are reported together with actual adherence to glucose monitoring. Changes in quality of life in different treatment groups were recorded monthly. Quality of life in patients on insulin was compared with those not taking insulin and absolute satisfaction with therapy gauged monthly. Individual questionnaire item scores and mean summed scores with SD for the DTSQ and WBQ questionnaires are reported.

All adverse events during the study were documented and any changes in safety parameters with rosiglitazone therapy recorded. Finally the outcomes attained in study patients were compared with

those achieved in routine general practice over the same timescale. Further cost-effectiveness analyses are planned but are outside the remit of this thesis.

5.6: Ethics, Funding and Indemnity

5.6.1: Ethical approval

Ethical approval was granted by the Central Oxfordshire Research Ethics Committee on 9th February 2000 and by the Aylesbury Vale Ethics Committee on 10th April 2000. A DDX license for rosiglitazone use within the feasibility study was obtained from the Department of Health on 25th April 2000.

5.6.2: Project funding and indemnity

The study was supported by a personal NHS SE R&D training fellowship award and DTU educational grant. Indemnity was provided by Oxford University and the practices involved.

5.6.3: Data handling

Case report forms (CRFs) were used to collect clinical data on study participants. Demographic details, concomitant medication, diabetes, medical and cardiovascular status were checked at study onset and closeout. Home blood glucose values, hypoglycaemia episodes, body weight, blood pressure, adherence, medication changes, adverse events and biochemical results were recorded monthly.

The data file repository (DFR) was used as the central database for all study data. This is a secure, password protected, validated, rule based system which monitors missing data. Copies of the case report forms returned by clinical centres were collated and all data was double punched into the DFR. Data was downloaded from the DFR and edited by myself before transfer to excel spreadsheets and statistical packages for analysis.

5.6.4: Study Documentation

A protocol detailing the background, design, objectives, methods and study outcomes was produced listing the administrative, clinical, pharmacological and biochemical tasks of the project. Detailed descriptions of algorithms, medications, clinic and educational procedures were included and details

for reporting of adverse events documented. 24-hour telephone contact was provided by myself. An A4 summary study protocol sheet was produced for all practices for quick reference purposes and to provide information for colleagues (see Appendix 1).

A operational resource manual was provided as a simplistic, rapid-reference practical guide to study procedures to enable nurses to implement the protocol-driven, treat-to-target approach. General information regarding patient recruitment, clinic preparation, equipment, visit schedules, therapy algorithms, data collection and adverse events was included at the beginning of this booklet. SOPs were developed for study procedures with explicit instructions for equipment preparation and tasks (blood pressure, venepuncture, BMI measurement and glucometer calibration). A detailed guide to study CRFs was provided as most practice nurses were unfamiliar with this form of data collection. The format of each sheet was explained, unique patient, nurse and practice identifiers discussed and completed samples provided. Missing data, missing visits and correction procedures were outlined and data handling procedures specified. The final section of the booklet provided detailed guidance to nurses on the gating mechanism for dose titrations within the six algorithms. Specific patient and therapy adjustment scenarios were rehearsed during the practice nurse training sessions using these notes.

Healthy living, diet, exercise and smoking cessation leaflets were designed exclusively for the study and were used together with existing Diabetes UK literature. Quick reference factfiles were provided for nurses listing the essential information required by patients and teaching plans were formulated for complex tasks. Appropriate patient leaflets were inserted in each visit section as a prompt and an alphabetical index for the resource manual and patient leaflets was included for ease of use.

Invitation letters to practices and patients, patient information sheets, study identification cards and appointment diaries were created. Blood glucose, food diaries and patient feedback questionnaires were designed specifically for use in the study. Each patient also received an individual treatment plan at baseline detailing the sequence of therapies that would be used if their blood glucose was elevated. All patient information received ethical approval prior to use.

The consent forms, CRFs, clinic notes, correspondence, laboratory result forms and data queries for each patient were organised in individual lever-arch blue subject folders with all forms situated in the order of use. This arrangement was designed to facilitate data collection, eliminate missing data and to reduce minimal administrative duties for practice nurses. Assay request forms, sample matrices, patient labels and biochemical schedules were supplied to each practice and stored

separately with the resource manual. Duplicate copies of all data forms were faxed to the DTU after clinics for checking and entry.

Section Three: Study Results

This section is divided into three chapters:

Chapter 6 focuses on the feasibility of using a nurse-led, protocol-driven, treat-to-target approach to glucose and CVS risk factor modification with early OHA combination and insulin to target basal and prandial glucose in primary care. Section 6.1 examines practice and patient participation data and compares demographic, clinical, biochemical and medical characteristics of recruited and non-recruited patients. Characteristics of the two groups are examined with the Appraisal of Diabetes (ADS) scale and the number and reasons for study withdrawals are listed. Section 6.2 examines the therapy use in the study and evaluates the number of agents required to attain normoglycaemia, the proportion of patients on maximal OHAs and the number of patients requiring insulin. Finally section 6.3 examines the acceptability of the program to patients in terms of their adherence, health perception and satisfaction with therapies, adverse events, safety issues and support required.

Chapter 7 focuses on the efficacy of the approach in terms of the overall degree of glucose lowering and CVS risk modification attained. Section 7.1 reports the fasting, prandial glucose, and HbA_{1c} lowering with the protocol-led, target-driven sequences and evaluates the proportion of patients that attain glucose targets with months from randomisation. Section 7.2 reports the changes in body weight that occur in the study. Systolic and diastolic blood pressure data is summarised in 7.3 and lipid data in 7.4. Finally overall cardiac risk is determined at the beginning and end of the approach. An estimate of the potential achievable effect of the protocol-led, target-driven approach is provided in the last section of this chapter by comparing the outcomes attained in the glucose study with those attained in non-recruited eligible patients in standard general practice care over the same period.

Finally chapter 8 provides an estimate of the differential effects of the potential therapy algorithms suggested for use in the large RCT of glucose optimisation and CVD in general practice. Primary therapy arms and individual sequences are examined to identify trends in efficacy with respect to glucose lowering, body weight, CVS risk modification, number of therapies needed and therapy satisfaction in patients. Potential limitations of this approach are discussed in chapter 9.

Chapter 6 : Feasibility of the Programme

6.1: Practice and patient participation

6.1.1: Recruitment of practices

20 practices in Oxfordshire and Buckinghamshire were approached to take part in the study. Seven practices (35%) agreed to participate. Of the 13 not recruited 8 had insufficient practice nurse time, 3 were unwilling due to time constraints, 1 was undergoing clinic reorganisation and 1 had insufficient patient numbers. The seven practices recruited were 19 Beaumont St practice, Oxford, Thame Health Centre, Wallingford Medical Centre, Morland House Surgery in Wheatley, Aston Clinton, Wendover and Bedgrove practices in Buckinghamshire

Table 6.1: Recruitment of practices

Practice	Recruited	Principal reason for non-participation
The Health Centre, Thame	Y	Recruited
Wallingford M/C, Wallingford	Y	Recruited
Morland House, Wheatley	Y	Recruited
19 Beaumont Street, Oxford	Y	Recruited
Aston Clinton Surgery (3 practices)	Y	3 practices recruited
28 Beaumont Street, Oxford	N	No practice nurse interest
Berinsfield H/C, Wallingford	N	Time constraints in practice
Bicester H/C, Coker Close	N	Rebuilding and space restrictions
Bletchingdon Road, Islip	N	No practice nurse interest
Carterton Surgery, Carterton	N	Insufficient T2DM patients
Cross Keys Practice, Princes Risboro'	N	No practice nurse time
Donnington H/C, Iffley Road	N	Time constraints in practice
58 Hollow Way, Cowley	N	No practice nurse time
Jericho Health Centre	N	No practice nurse time
Faringdon Health Centre	N	No practice nurse time
Kidlington H/C, Oxford Road	N	No practice nurse time
Malt House Surgery, Abingdon	N	No practice nurse time
Marston M/C, 24 Cherwell Drive	N	Time constraints in practice
Total practices contacted : 20	**7**	**Practice recruitment rate : 35%**

6.1.2: Recruitment of patients

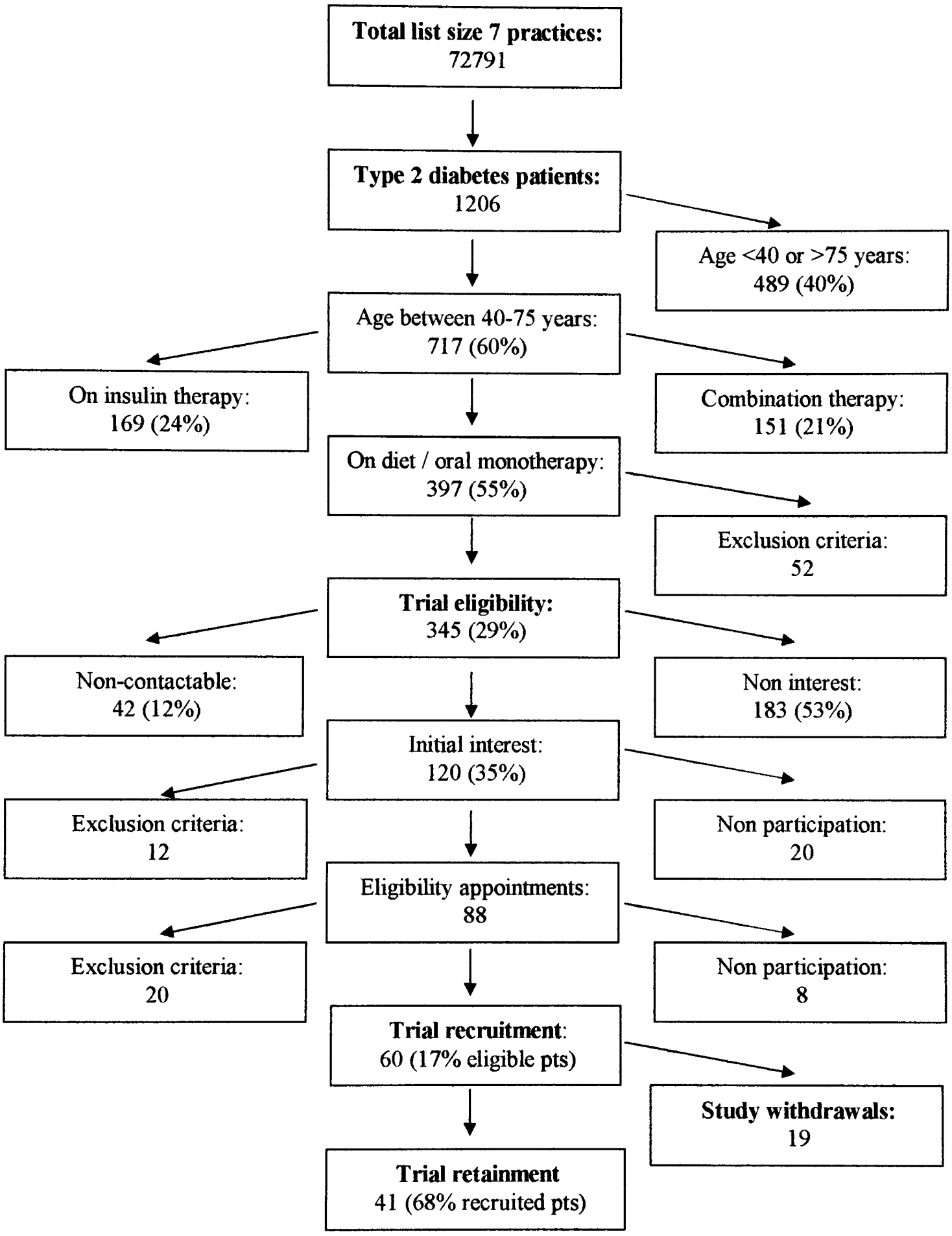
The total list size of patients within the seven practices was 72791. Of these 1206 patients with type 2 diabetes were identified from practice registers giving an estimated prevalence of diabetes of 1.7%. 717 of these patients fulfilled the study age criteria and 397 fulfilled the treatment criteria. 489 patients were aged <40 or >75 years of age, 169 were already taking insulin, 151 were receiving combination agents and 52 had other exclusion criteria present. 345 (29%) patients were thus eligible for study inclusion.

120 patients expressed initial interest in the study when contacted by telephone, 183 were not interested and 42 were non-contactable. 33 of the 120 were subsequently found to possess exclusion criteria not identifiable from computer records and 27 declined participation. 60 patients were recruited to the study and randomised to medication.12 patients were recruited from Thame practice, 11 from Wallingford and Wheatley, 9 from 19 Beaumont Street, 7 from Aston Clinton/ Wendover and 10 from Bedgrove. The recruitment process in each practice is highlighted in table 6.2 below and figure 6.1 overleaf.

Table 6.2: Recruitment of patients within practices

Practice	List Size	T2DM	Eligible (%)	Interested (%)	Recruited (%)
Thame	11105	205 (1.8%)	57 (28)	18 (9)	12 (6)
Wallingford	14246	250 (1.8%)	62 (25)	22 (9)	11 (4)
Wheatley	9623	165 (1.7%)	53 (32)	27 (16)	11 (7)
Beaumont St	11947	113 (0.9%)	31 (27)	15 (13)	9 (8)
Aston Clinton	5122	87 (1.7%)	20 (23)	9 (10)	4 (5)
Wendover	11125	190 (1.7%)	49 (26)	10 (5)	3 (2)
Bedgrove	9623	196 (2.0%)	73 (37)	19 (10)	10 (5)
Total	72791	1206 (1.7%)	345 (29)	120 (10)	60 (5)

Figure 6.1 : Consort diagram: Overview of patient recruitment



6.1.3: Factors influencing patient participation

The principal barriers to recruitment were established in all non-interested patients. These reasons are summarised in table 6.3 below:

Table 6.3 : Principal reasons for non-participation (n = 225)

Reasons for Non Participation	N=225	%	95% CI
Access			
Clinics in working hours	35	16	
Cannot get to surgery	5	2	
Appointment day inconvenient	7	3	
Moving away from the practice area	8	4	
	55	**25**	**19-30**
Time and Effort			
Too much effort involved	23	10	
Too much time needed	20	9	
	43	**19**	**14-24**
Therapy			
Unwilling to change current therapy	34	15	
Unwilling to take insulin injections	21	9	
Unwilling to monitor home glucose values	3	1	
Unwilling to take increased therapies	2	1	
	60	**26**	**21-32**
Other Reasons			
Currently unwell*	19	8	
Other**	6	3	
Non-contactable at registered address	42	19	
	67	**30**	**24-36**

* Family bereavement 4, personal illness 15

** DVLA implications 4, lifestyle too erratic 1, not aware of diabetes diagnosis 1

The principal reasons for non-participation were work commitments (16%), resistance to therapy changes (15%), resistance to using insulin (9%) and energy (10%) or time commitments (9%).

6.1.4: Baseline characteristics of recruited and non-recruited patients

60 patients were recruited to the study. Their mean age was 60.9 years, mean HbA_{1c} at baseline 7.5%, mean BMI was 30.5kg/m^2 and median duration of diabetes 3 years. 65% of recruited patients were male and 35% female. 37% were on diet alone, 38% were taking sulphonylurea and 25% metformin therapy. 50% had documented hypertension, 25% hyperlipidaemia, 12% IHD, 2% PVD, 7% retinopathy and 3% nephropathy at baseline. 30% were never smokers, 53% ex-smokers and 17% current smokers. Their mean BP was 144/84mmHg and mean total-cholesterol 5.1mmol/L.

In contrast 285 patients were not recruited to the study. Their mean age was 60.3 years, mean HbA_{1c} at baseline was 7.8%, mean BMI was 30.3kg/m^2 and median duration of diabetes 4 years. 62% were male and 38% female. 33% were on diet alone, 37% were taking sulphonylurea and 26% metformin therapy. 43% had documented hypertension, 13% hyperlipidaemia, 23% IHD, 1% PVD, 8% retinopathy and 3% nephropathy at baseline. 40% were never smokers, 15% ex-smokers, 20% current smokers and 25% had unknown smoking status. Their mean BP was 147/83mmHg and mean total-cholesterol 5.5mmol/L. This data is shown in table 6.4 below.

The baseline characteristics of recruited and non-recruited patients in this study were thus similar with only diabetes duration, smoking status and complications differing significantly between the groups. Despite the significantly shorter duration of T2DM in recruited subjects, significantly more hyperlipidaemia and coronary heart disease were reported amongst recruited patients.

Table 6.4 : Baseline Characteristics of Recruited and Non Recruited Patients

	Recruited (n = 60)	Non-Recruited (n = 285)	P Value
Demographic			
Gender (M/F)	39/21	176/109	0.64
Age (years)*	60.9 (8.2)	60.3 (9.6)	0.61
Clinical			
Weight (kg)*	89.0 (14.8)	87.8 (18.7)	0.58
Body mass index (kg/m^2)*	30.5 (4.9)	30.3 (5.7)	0.68
Systolic blood pressure (mmHg)*	144 (17.2)	147 (20.7)	0.21
Diastolic blood pressure (mmHg)*	84 (10.9)	83 (10.8)	0.52
Diabetes duration (years)†	3.0 (1.0-5.0)	4.0 (2.0-7.0)	0.021
Documented hypertension (%)	50.0	42.8	0.31
Documented hyperlipidaemia (%)	25.0	13.3	0.020
Documented cardiovascular disease (%)	15.0	9.2	0.016
Tobacco smoking (%) never/ex/current/unknown	30/53/17/0	40/15/20/25	<0.0001
Excessive alcohol intake (%)	0.0	9.0	1.00
Biochemical			
HbA_{1c} (%)*	7.5 (0.9)	7.8 (1.7)	0.12
Fasting Plasma Glucose (mmol/L)*	8.1 (2.9)	9.6 (3.8)	<0.0001
Plasma Creatinine (μmol/L)‡	84.3 (69.3-102.5)	89.4 (69.5-115)	0.31
Alanine Transaminase (IU/L)‡	28.2 (17.3-45.9)	--	--
Total Cholesterol (mmol/L)*	5.1 (1.1)	5.5 (1.1)	0.038
LDL-Cholesterol (mmol/L)*	3.2 (0.9)	--	--
HDL-Cholesterol (mmol/L)*	1.2 (0.4)	--	--
Triglyceride (mmol/L)‡	1.5 (0.8-3.0)	2.2 (1.2-4.0)	0.15
Urine albumin†	15 (6-38)	--	--
Documented Existing Complications			
Retinopathy (%)	4 (6.7)	23 (8.1)	1.00
Neuropathy (%)	0 (0.0)	4 (1.4)	1.00
Ischaemic Heart Disease (%)	9 (15.0)	26 (9.1)	0.21
Peripheral Vascular Disease (%)	1 (1.7)	3 (1.1)	0.54
Nephropathy (%)	2 (3.3)	7 (2.5)	0.66
Medication			
Diabetes (%) diet /metformin /sulphonylurea/combn	37/25/38/0	33/26/37/4	0.91

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

6.1.5: Comparison of baseline characteristics of recruited patients by therapy group

A comparison of baseline demographic characteristics of recruited patients by allocated therapy group is provided in table 6.5. 22 patients were randomly allocated to the metformin, 21 to the rosiglitazone and 17 to the glipizide therapy arms using the central randomisation programme. Minimisation criteria were used to ensure balanced distribution across groups. Baseline demographic characteristics of patients in each therapy arm were similar for almost all variables

with the exception of HbA_{1c}, FPG and TG. All of these were significantly higher in the glipizide than the metformin or rosiglitazone arms.

Table 6.5 : Baseline Characteristics of Recruited Patients by Therapy Group

	Metformin (n = 22)	Rosiglitazone (n = 21)	Glipizide (n = 17)	P Value
Demographic				
Gender (M/F)	15/7	13/8	10/7	0.80
Age (years)*	60.7 (9.0)	63.3 (7.6)	58.3 (7.5)	0.17
Clinical				
Weight (kg)*	87.6 (15.5)	86.5 (13.7)	93.8 (14.9)	0.28
Body mass index (kg/m^2)*	30.0 (3.8)	29.9 (5.2)	32.2 (5.7)	0.29
Systolic blood pressure (mmHg)*	141.1 (16.7)	144.5 (19.6)	145.6 (15.3)	0.70
Diastolic blood pressure (mmHg)*	83.0 (10.0)	84.6 (12.5)	85.2 (10.4)	0.81
Diabetes duration (years)†	2.0 (1.0-5.0)	3.0 (2.0-4.0)	3.0 (2-8)	0.62
Documented hypertension (%)	31.8	66.7	52.9	0.07
Documented hyperlipidaemia (%)	18.2	33.3	23.5	0.51
Documented cardiovascular disease (%)	18.2	14.3	11.8	0.41
Tobacco smoking (%) never / ex / current	36/55/9	19/62/19	35/41/24	0.50
Biochemical				
HbA_{1c} (%)*	7.1 (0.7)	7.6 (0.8)	8.0 (0.9)	0.0030
FPG (mmol/L)*	6.9 (1.4)	8.3 (1.7)	9.4 (3.1)	0.0020
Plasma Creatinine (μmol/L)‡	87 (71-107)	83 (67–102)	83 (70-98)	0.71
Alanine Transaminase (IU/L)‡	28 (18-42)	29 (17-48)	28 (16-49)	0.22
Total Cholesterol (mmol/L)*	5.2 (1.3)	4.9 (0.8)	5.3 (1.1)	0.45
LDL-Cholesterol (mmol/L)*	3.3 (0.9)	3.1 (0.7)	3.1 (1.0)	0.75
HDL-Cholesterol (mmol/L)*	1.3 (0.5)	1.3 (0.3)	1.1 (0.2)	0.30
Triglyceride (mmol/L) ‡	1.3 (0.7-2.6)	1.3 (0.8-2.2)	2.2 (1-4.9)	0.035
Urine albumin†	15 (6-54)	16 (6-25)	12 (6-38)	0.98
Diabetes Complications				
Retinopathy (%)	0 (0.0)	2 (9.1)	2 (11.8)	--
Neuropathy (%)	0 (0.0)	0 (0.0)	0 (0.0)	--
Ischaemic heart disease (%)	4 (18.2)	3 (14.3)	2 (11.8)	--
Peripheral vascular disease (%)	0 (0.0)	0 (0.0)	1 (5.9)	--
Nephropathy (%)	2 (9.1)	0 (0.0)	0 (0.0)	--
Medication				
Diabetes (%) diet / metformin / surea	32/45/23	48/38/14	29/29/41	0.34

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

6.1.6: Study withdrawals

41 (68%) patients successfully completed the study with 19 (32%) withdrawing before completion. The timing and reasons for study withdrawal are shown in table 6.6 below.

Despite prior consent six patients withdrew as a result of an unwillingness to commence insulin therapy. One patient was concerned that his DVLA licence would be withdrawn whilst the others believed that their degree of glucose control did not warrant injections. These patients predominantly withdrew between study visits five and nine and were equally distributed between therapy groups.

Side effects from medications were responsible for seven withdrawals. Three patients experienced gastrointestinal side effects with metformin, two patients arthralgia with rosiglitazone, one patient ankle oedema with rosiglitazone and finally one patient withdrew because of grade 3 hypoglycaemia with study medication. The majority of these withdrawals occurred between visits four and seven.

Three patients perceived that their blood glucose control was inadequate in the study and withdrew. One was unable to tolerate blood glucose monitoring and two felt that their control was too slow or had worsened with study therapy. These withdrawals occurred between visits three and six.

Finally three patients discontinued participation as a result of other reasons; one due to stress, one as a result of personal problems and one moved away from the region.

6.1.7: Comparison of characteristics of completing and withdrawing patients

A comparison of the baseline demographic characteristics of patients who completed and withdrew from the study is provided in table 6.7 overleaf. These two groups of patients were similar in almost all respects but a significant difference in diabetes duration was noted. Patients who withdrew from the study had significantly greater duration of diabetes than those who completed.

Table 6.6 : Study withdrawals

Reason for Study Withdrawal	Number	Therapy	Visit
Refusal to commence insulin therapy			
• Wouldn't commence insulin therapy	1	A	6
• Would lose DVLA licence	1	A	9
• Wouldn't commence insulin therapy	1	B	5
• Wouldn't commence insulin therapy	1	C	6
• Wouldn't commence insulin therapy	1	E	5
• Wouldn't commence insulin therapy	1	E	6
Side effects from medication			
• Diarrhoea with metformin	1	A	5
• Abdominal discomfort with metformin	1	B	5
• Diarrhoea with metformin	1	B	6
• Angina / arthralgia with rosiglitazone	1	D	5
• Ankle oedema with rosiglitazone	1	D	4
• Arthralgia with rosiglitazone	1	D	5
• Grade 3 hypoglycaemia	1	D	7
Inadequate blood glucose control			
• Blood glucose worsened with study therapy	1	A	6
• Blood glucose control too slow	1	D	4
• Unable to tolerate HBGM testing	1	F	3
Miscellaneous reasons			
• Stress	1	B	3
• Personal problems	1	C	3
• Moved away from Oxford	1	D	5
Total	**19**	-	-

Table 6.7 : Baseline characteristics of patients who completed and withdrew from the study

	Completed (n = 41)	Withdrew (n = 19)	P Value
Demographic			
Gender (M/F)	28/13	10/9	0.24
Age (years)*	61.2 (8.5)	60.4 (7.7)	0.75
Randomisation			
AB / CD / EF	14/13/14	8/8/3	0.57
Clinical			
Weight (kg)*	89.4 (13.5)	88.0 (17.6)	0.73
Body mass index (kg/m^2)*	30.3 (5.1)	31.1 (4.6)	0.55
Systolic blood pressure (mmHg)*	144.7 (15.7)	141.2 (20.3)	0.47
Diastolic blood pressure (mmHg)*	84.7 (10.4)	83.1 (12.2)	0.59
Diabetes duration (years)†	2.0 (1.0-4.0)	4.0 (3.0-6.5)	0.019
Documented hypertension (%)	53.7	42.1	0.40
Documented hyperlipidaemia (%)	22.0	31.6	0.42
Documented cardiovascular disease (%)	9.8	26.3	0.37
Tobacco smoking (%) never / ex / current	24/59/17	42/42/16	0.36
Excessive alcohol intake (%)	0.0	0.0	1.00
Biochemical			
HbA_{1c} (%)*	7.4 (0.9)	7.7 (0.7)	0.30
FPG (mmol/L)*	8.3 (2.5)	7.5 (1.5)	0.20
Plasma Creatinine (μmol/L)‡	85 (70-103)	83 (67-102)	0.69
Alanine Transaminase (IU/L)‡	28 (18-44)	28 (16-51)	0.96
Total Cholesterol (mmol/L)*	5.1 (1.1)	5.3 (0.9)	0.49
LDL-Cholesterol (mmol/L)*	3.1 (1.0)	3.2 (0.7)	0.72
HDL-Cholesterol (mmol/L)*	1.2 (0.3)	1.3 (0.5)	0.073
Triglyceride (mmol/L) ‡	1.6 (0.8-3.2)	1.4 (0.7-2.8)	0.52
Urine albumin†	16 (6-38)	11 (6-31.5)	0.83
Diabetes Complications			
Retinopathy (%)	4 (9.8)	0 (0.0)	0.30
Neuropathy (%)	0 (0.0)	0 (0.0)	1.00
Ischaemic heart disease (%)	3 (7.3)	6 (31.6)	0.095
Peripheral vascular disease (%)	1 (2.4)	0 (0.0)	1.00
Nephropathy (%)	2 (4.9)	0 (0.0)	1.00
Medication			
Diabetes (%) diet / metformin / sulphonylurea	34/37/29	42/42/16	0.53

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

6.1.8: ADS Characteristics of Interested and Non-Interested Patients

87% of interested patients and 70% of non-interested patients completed the ADS questionnaire scale. The table below compares the characteristics of patients who were interested in taking part in the study with those who were not.

Interested patients were more upset (RR1.6, 95%CI: 0.97,2.54) and uncertain about diabetes (RR1.8 (1.17, 2.65)), were coping less well, (RR0.6 (0.42, 1.03)), were more likely to consider their diabetes would worsen (RR2.3 (1.33, 3.84)) and had a more external locus of glucose control (RR1.6 (1.06, 2.39)) than non-interested patients.

Table 6.8 : ADS Results

Questionnaire Item	ADS Categories Compared	Risk Ratio	95% CI
1. Upset	Very / Extreme vs Not at All	1.6	(0.97, 2.54)
2. Control	Total vs None / Slight	0.66	(0.42, 1.03)
3. Uncertainty	Large / Extreme vs None	1.76	(1.17, 2.65)*
4. Life goals	Very / Extreme vs Not at all	1.66	(0.72, 2.75)
5. Locus	External / Internal	1.59	(1.06, 2.39)*
6. Coping	Extremely vs No / Slight	0.80	(0.48, 1.34)
7. Worsening	Very/Extremely vs Not likely	2.26	(1.33, 3.84)*

* $p < 0.05$

6.2. Therapy Use

This section describes use of therapies with time from randomisation. The mean number of therapies is calculated together with the proportion of patients on 0,1,2 and 3 therapies and number taking maximal OHA doses. The proportion of patients requiring additional isophane or humalog insulin is also evaluated. A comparison of therapy use within different therapy algorithms in the RCT study is provided in chapter 8.

6.2.1: Mean number of therapies

The mean number of therapies increased from 0.7 at baseline to 2.4 at one year, with the greatest increase in the number of therapies occurring in the first 6 months. At visit 8 the mean number of therapies taken by patients was 2.1.

6.2.2: Proportion of patients on multiple therapies

The proportion of patients on multiple therapies increased throughout the study. 33% of patients were treated with diet alone before the study whilst 67% received monotherapy. Therapies were increased in almost all patients at study onset. 95% of patients received monotherapy, 2% were treated with 2 agents and only 3% remained on diet alone. By 3 months only 2% remained on diet, 44% on monotherapy, 50% had commenced prandial therapy and 4% were taking 3 therapies. Between 4 and 5 months 2% of patients took 4 therapies but the fourth agent (acarbose) was very poorly tolerated and from 6 months the maximum number of agents used was 3. At 6 months 21% patients took 3 therapies, 60% took 2 and 19% were on monotherapy. By 12 months the respective figures were 51%, 34% and 15%. This data is represented in figure 6.2.

6.2.3: Insulin Use

24 patients were successfully commenced on isophane in the study and 16 on humalog. At one year 9 patients were using isophane alone, 1 patient humalog alone and 15 patients both insulins. These results are displayed in table 6.9 and figure 6.3 below.

Table 6.9: Number (ITT%) of patients on insulin therapy

Months	Isophane	Humalog	Both Insulins	Neither Insulin
0	0 (0%)	0 (0%)	0 (0%)	60 (100%)
3	2 (3%)	8 (13%)	1 (2%)	49 (82%)
6	8 (13%)	8 (13%)	3 (5%)	41 (68%)
9	6 (10%)	2 (3%)	14 (23%)	38 (63%)
12	9 (15%)	1 (2%)	15 (25%)	35 (58%)

Figure 6.2: Mean number of therapies taken with time from randomisation:

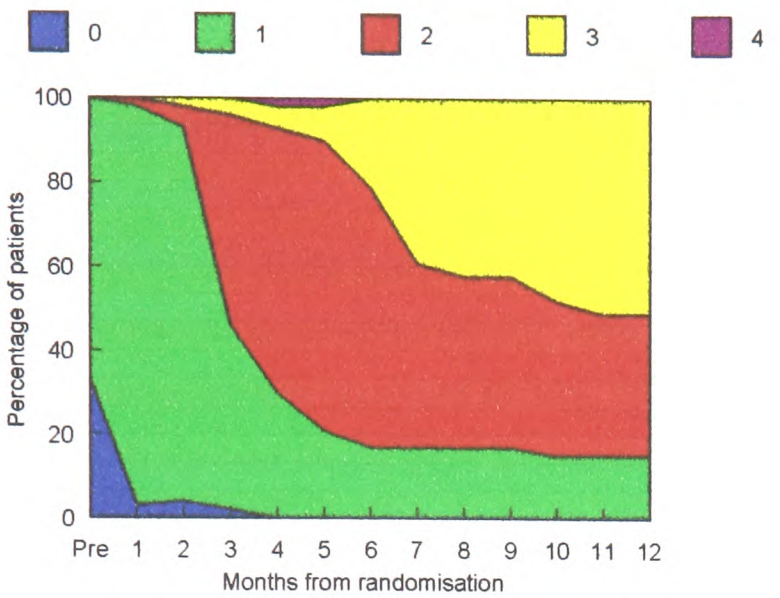
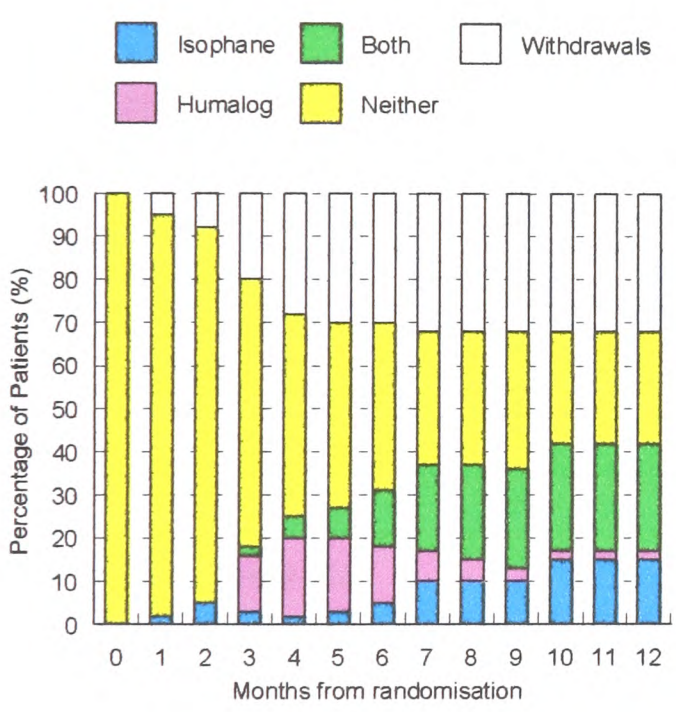


Figure 6.3: Insulin Use:



Section 6.3: Acceptability, Adherence and Safety Issues

This section evaluates the acceptability of the glucose programme in practices by evaluating the tolerability and safety of therapeutic regimes. Adherence, therapy satisfaction and health perception of patients are reported and views of nurses and patients towards the programme gauged. Subjective diet, exercise, monitoring and therapy adherence reports obtained using the Summary of Diabetes Self-Care Activities scale are compared with meter glucose results and food diary analysis.

6.3.1: Dietary Adherence

35% of patients reported full adherence, 62% usual adherence and 3% some adherence to dietary guidance at baseline. These figures decreased during the year to 25%, 58% and 17%. No patients reported consistent non-adherence to dietary guidance in the study.

Decreased adherence to high fibre foods but increased adherence to low fat foods was seen with time from randomisation. 22% always adhered, 60% usually adhered and 18% sometimes adhered to a high fibre diet at baseline compared to 15%, 62% and 23% at 1 year. The proportion of patients who always consumed a low fat diet increased from 15% at baseline to 22% at one year.

Table 6.10: Baseline Food Diary Data

Variable	All Therapies Mean (SD)	Metformin Mean (SD)	Rosiglitazone Mean (SD)	Glipizide Mean (SD)
Number of meals/3days	17 (3)	17 (3)	17 (3)	17 (3)
Total energy kcal/day	2090 (599)	2121 (669)	1921 (441)	2257 (651)
Protein Intake g/day	86 (23)	87 (28)	79 (16)	92 (24)
Fat Intake g/day	83 (29)	81 (28)	79 (29)	92 (29)
CHD Intake g/day	242 (66)	251 (78)	226 (51)	252 (64)
EtOH g/day	13 (24)	16 (24)	8 (14)	17 (33)
Monosat Fat g/day	29 (11)	28 (10)	27 (10)	32 (12)
Polyunsat Fat g/day	16 (8)	18 (9)	16 (8)	15 (7)
Saturated Fat g/day	29 (11)	30 (11)	26 (11)	30 (11)
Fibre g/day	25 (8)	26 (8)	24 (6)	24 (9)
Dietary Cholesterol	293 (142)	276 (131)	306 (157)	299 (143)

(EtOH: 1 unit = 9g ethanol)

6.3.2: Exercise Adherence

Exercise adherence increased during the study from 25% always adherent, 28% usually adherent, 30% sometimes adherent and 18% never adherent to guidance at onset to 32%, 17%, 37% and 15% at one year.

6.3.3: Therapy Adherence

Reported therapy adherence in the study was high with 79% of patients reporting full adherence to basal therapy at baseline and 60% at one year with intention to treat analyses. 10% of patients were

usually adherent and 2% sometimes adherent to basal therapy at baseline compared to 5% and 4% at one year. No patients reported total non-adherence to basal therapy during the study.

Reported adherence to prandial therapy was similar with 55% of all patients reporting full adherence to prandial therapy at one year with intention to treat analyses. Reported ITT adherence to isophane insulin was 51% at one year.

6.3.4: Glucose monitoring adherence

Adherence to home blood glucose monitoring was high with 88% of patients adherent at baseline and 98% / 67% adherent at one year with valid case and intention to treat analyses respectively. The mean number of profiles remained relatively constant during the study at 7.5 (2.4) mirroring closely the recommended protocol levels. Problems with meter records or computer downloads within practices were responsible for all the missing data in the latter part of the study. These data are summarised in table 6.11 below.

Table 6.11: Glucose Monitoring Adherence:

Month	N Pts	N Pt Tests	VC %	ITT %	N tests scheduled	Actual mean (SD) profiles per visit
1	60	53	88	88	4	3.3 (1.4)
2	57	53	93	88	8	7.5 (2.4)
3	55	52	95	87	8	7.4 (2.5)
4	48	47	98	78	8	7.8 (2.8)
5	43	43	100	72	8	7.7 (3.3)
6	42	41	98	68	8	7.3 (3.0)
7	42	41	98	68	8	7.3 (2.6)
8	41	41	100	68	8	7.5 (2.6)
9	41	41	100	68	8	7.8 (2.7)
10	41	40	98	67	8	8.5 (3.4)
11	41	40	98	67	8	8.5 (3.0)
12	41	40	98	67	8	7.5 (2.3)

6.3.5: Principal Reasons for Non-Adherence

Detailed reasons for non-adherence were not reported but almost all patients when asked about non-adherence stated that the recommendations were not conducive to their lifestyle. Foreign business travel, shift work, religious festivals and intercurrent illness were the major reasons for protocol non-adherence Motivation and time constraints were the principal reasons for exercise non-adherence. Prandial glucose monitoring was performed less well than basal records. Particular problems included inaccurate timing of the two-hour postprandial interval or late evening meals precluding the pre-bedtime record.

Quality of Life

This section reports patient QoL during the one year study. Health perception scores, wellbeing, treatment satisfaction and views about the study are reported. Paired ttest comparisons of the entire group at baseline and one year are shown together with ANOVA analyses to compare differences between therapy groups. Results are shown in figures below.

6.3.6: Health Perception Score

The mean health perception of patients in the study was high and changed little during the study from 80% at baseline to 82% at one year (p=0.54). The differences in health perception between groups were small but the greatest increase was seen in the metformin therapy groups (83% to 88%) followed by rosiglitazone groups (76% to 80%). Health perception in the glipizide therapy groups declined from 80 to 79% during the study period. A decrease in health perception in all groups was seen between 4-6 months, consistent with the time during which insulin was commenced. Health perception appeared to be related to adverse effects of therapy and symptoms of hyperglycaemia but was also affected by events and intercurrent illness unrelated to the study.

6.3.7: Treatment Satisfaction Score

Treatment satisfaction scores were high during the study and remained constant throughout the year. No significant change in treatment satisfaction was seen over the year (p=0.87) with a mean therapy satisfaction score of 30/36 (83%) at baseline and 31/36 (86%) at one year. Satisfaction increased slightly in metformin (86% to 92%) and rosiglitazone arms (83% to 89%) but remained constant in the glipizide arm (81%). No significant differences between therapy groups was seen (p=0.37) and no significant difference between insulin and non-insulin users was observed (p=0.07).

14% of patients perceived their baseline glucose values to be mostly elevated, 29% sometimes, 33% occasionally and 24% never elevated. At 1 year 5% considered their glucose values were mostly elevated, 31% sometimes, 38% occasionally and 26% never elevated. In contrast 8% perceived their glucose values to be unacceptably low for most of the time, 5% sometimes, 29% occasionally and 57% never at baseline. At 1 year 5% considered their glucose to be unacceptably low for most of the time, 15% sometimes, 36% occasionally and 43% never.

6.3.8: Wellbeing Scores

Positive wellbeing remained high through the study with no significant difference between baseline and one year values (7.98 and 8.42 respectively). No significant differences between therapy groups were seen although a non-significant trend towards increased positive wellbeing in the glipizide and rosiglitazone groups through the year was observed. Levels of anxiety and depression were low and not increased during the study and energy remained relatively high throughout (mean baseline score 6.80, mean one year score 7.15). Once again no significant differences during the study or between therapy groups were seen.

6.3.9: Patients perceptions of the study

Detailed feedback was obtained from 65% of all recruited patients regarding their experiences of the study and their views about future diabetes care. 44% of patients felt the study was extremely useful in helping them manage their diabetes, 41% felt it had been very useful and 8% thought it had been moderately useful. Only 8% of patients reported that it had been slightly or not at all useful to their diabetes management. The educational leaflets provided by the study were also highly valued. 79% of patients had found them extremely or very useful, 21% reported them to be moderately useful and no patients felt they were not at all useful or only slightly useful. Equally the monthly clinic appointments were highly rated. 41% of patients felt they were extremely useful, 46% very useful and 13% moderately useful. No patients reported the clinic appointments to be only slightly useful or not at all useful. The home blood glucose testing included in the study was felt by patients to be very useful to their understanding of glucose control in T2DM. 41% of respondents reported it to be extremely useful, 49% very useful and 10% moderately useful. No patients found the monitoring slightly or not at all useful.

Provision of the pre-specified treatment plans at the beginning of the study was also highly regarded by respondents. 78% found this extremely or very useful whilst 26% reported it to be moderately

useful.When asked how difficult it was to take more tablets for their diabetes 69% respondents reported it to be not at all difficult. 10% found it slightly difficult, 15% moderately difficult and 5% very difficult. 38% of respondents felt slightly anxious about the possibility of needing insulin therapy in the study, 18% were moderately anxious, 15% very anxious and 15% extremely anxious. For those patients who commenced insulin therapy the majority (76%) found the education extremely or very useful and 18% reported it to be moderately useful. 95% patients felt that their understanding of T2DM had improved as a result of taking part in the study.

Table 6.12: Mean Health Perception (%) with months from randomisation:

Time(months)	N	All Therapies	Met Arm	Rosi Arm	Glip Arm
0	60	80	83	76	80
3	48	79	80	80	79
6	42	79	80	78	77
9	41	80	85	81	73
12	41	82	88	80	79

Paired ttest: T = -0.62 p = 0.54 **ANOVA:** F = 1.23 p = 0.30

Table 6.13: Mean Treatment satisfaction score (Range 0 – 36):

Time (months)	N	All Therapies	Met Arm	Rosi Arm	Glip Arm
0	60	30	31	30	29
3	48	31	30	31	31
6	42	32	32	32	30
9	41	31	33	32	29
12	41	31	33	32	29

Paired ttest: T = 0.17 p = 0.87 **ANOVA:** F = 1.01 p = 0.37

Table 6.14: Mean Treatment satisfaction score in insulin versus non-insulin treated patients:

Time (months)	N	All Therapies	Insulin Users	Non Insulin Users
0	60	30	31	30
3	48	31	32	31
6	42	32	30	33
9	41	31	30	33
12	41	31	30	33

Paired ttest: T = 0.17 p = 0.87 **ANOVA:** F = 3.50 p = 0.069

Table 6.15a: Mean depression score with months from randomisation (Range 0 – 6)

Time (months)	N	All Therapies	Met Arm	Rosi Arm	Glip Arm
0	60	0.80	0.59	0.48	1.47
3	48	0.77	0.78	0.50	1.00
6	42	0.74	0.73	0.31	1.14
9	41	0.54	0.36	0.54	0.71
12	41	0.75	0.55	0.57	1.24

Paired ttest: T = 0.55 p = 0.58 **ANOVA:** F = 1.05 p = 0.36

Table 6.15b: Mean anxiety score with months from randomisation (Range 0 – 6)

Time (months)	N	All Therapies	Met Arm	Rosi Arm	Glip Arm
0	60	0.52	0.45	0.29	0.88
3	48	0.51	0.39	0.43	0.73
6	42	0.52	0.60	0.23	0.71
9	41	0.54	0.50	0.23	0.86
12	41	0.62	0.41	0.48	1.06

Paired ttest: T = -1.23 p = 0.22 **ANOVA:** F = 0.93 p = 0.40

Table 6.15c: Mean energy score with months from randomisation (Range 0 – 12)

Time (months)	N	All Therapies	Met Arm	Rosi Arm	Glip Arm
0	60	6.80	7.27	6.76	6.24
3	48	7.28	7.28	7.86	6.73
6	42	6.90	6.73	6.85	7.14
9	41	7.00	6.86	7.54	6.64
12	41	7.15	7.36	7.19	6.82

Paired ttest: T = -1.40 p = 0.17 **ANOVA:** F = 0.33 p = 0.72

Table 6.15d: Mean positive wellbeing score with months from randomisation (Range 0 – 12)

Time (months)	N	All Therapies	Met Arm	Rosi Arm	Glip Arm
0	60	7.98	8.27	7.57	8.12
3	48	7.72	7.33	8.14	7.80
6	42	7.79	7.60	7.62	8.14
9	41	8.07	7.50	8.31	8.43
12	41	8.42	8.27	8.57	8.41

Paired ttest: T = -1.28 p = 0.21 **ANOVA:** F = 0.80 p = 0.45

Figure 6.4: Mean health perception (%): Perception = 78.9 + 0.16 Months Slope p = 0.12

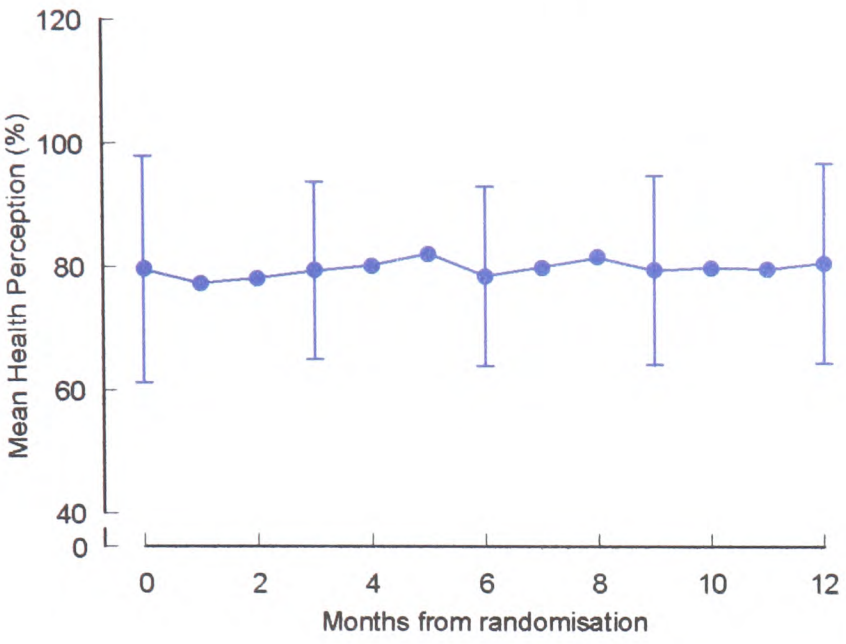


Figure 6.5: Mean treatment satisfaction score: Satisfaction = 30.8 + 0.05 Months p = 0.47

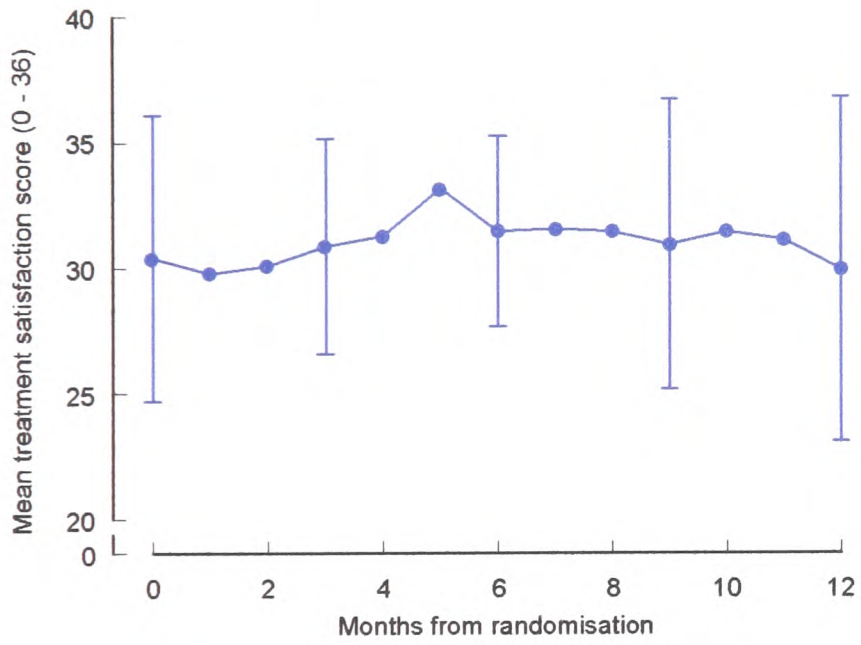
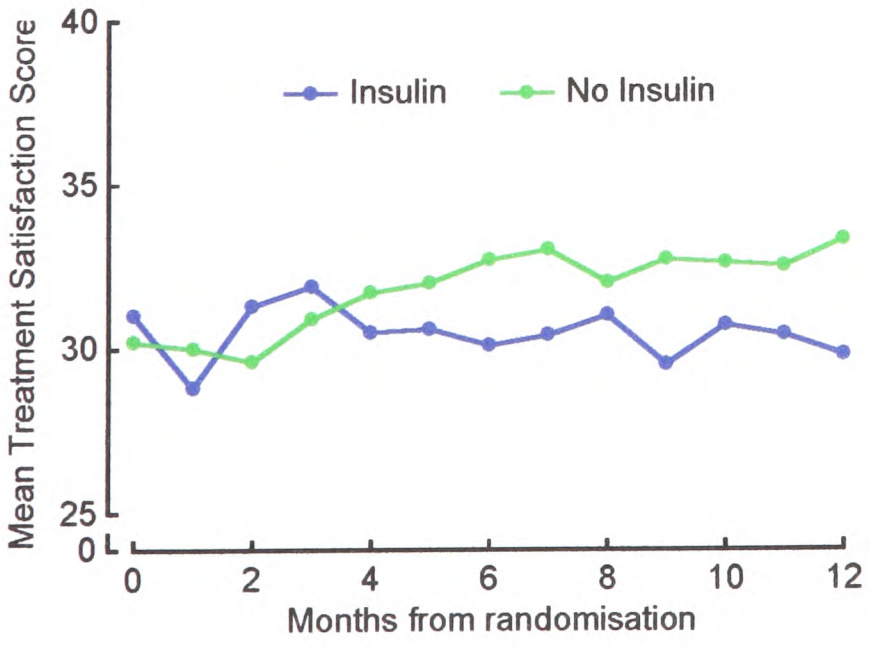


Figure 6.6: Mean treatment satisfaction score with respect to insulin use:



6.3.10: Safety Data

The safety of rosiglitazone in the study was assessed using six monthly haemoglobin measurements and monthly ALT results. The hepatotoxicity safety criterion used was an ALT level more than one and a half times the upper limit of the normal range and for anaemia Hb <11.5g/dL.

No significant differences in mean baseline Hb between therapy groups were observed. The mean baseline Hb in females was 14.5 in the metformin arm, 14.0 in the rosiglitazone arm and 13.4 in the glipizide group. The mean delta Hb was greater in the rosiglitazone arm (–1.2g/dL) than the metformin (–0.4g/dL) or glipizide (–0.3g/dL) groups and the proportion of patients whose Hb decreased below 11.5g/dL during the study was greater in the rosiglitazone (25%) than the metformin (0%) or glipizide therapy groups (0%). These trends were not statistically significant (F=2.37 p=0.10).

In males the mean baseline Hb was 15.3 in the metformin arm, 15.2 in the rosiglitazone group and 15.4 in the glipizide arm. The mean delta Hb was again greater in the rosiglitazone arm (-0.8g/dL) than the metformin (-0.6g/dL) or glipizide (-0.1g/dL) groups. The proportion of patients whose Hb decreased below 11.5g/dL was 20% in the metformin arm, 23% in the rosiglitazone group and 0% in the glipizide arm.

The greatest change in Hb in females occurred in therapy groups C and D with mean deltas at one year of –2.0 and –1.0g/dL respectively. In males the greatest change occurred in groups B, C and D with mean deltas of –0.8, -0.7 and –0.9g/dL respectively. The greatest increase in the proportion of patients with Hb<11.5g/dL at study closeout was 33% in therapy group D in females and therapy group C in males.

No significant differences between mean baseline ALT were observed between therapy groups but a significantly greater mean delta ALT reduction was seen with rosiglitazone –7.3 compared to metformin –1.8 or glipizide –2.1 arms. The proportion of patients with ALT above the safety criterion decreased in all groups throughout the study from 14% to 5% in the metformin and rosiglitazone arms and 18% to 12% in the glipizide groups. The greatest mean delta in the individual treatment sequences occurred in C at –11.3. No increased hepatotoxicity with rosiglitazone was observed in the study.

Table 6.16: Haemoglobin Results Males : Primary Therapy Groups

Therapy Sequence	N	Baseline Hb (g/dl)	Mean Δ Hb (g/dl)	% Pts with Hb <13.5g/dl at baseline	% Pts with Hb <13.5 g/dl at one year
Met Arm	15	15.3	-0.6	7	20
Ros Arm	13	15.2	-0.8	23	23
Glip Arm	10	15.4	-0.1	0	0
Total	38	15.3	-0.5	11	16

ANOVA: F = 1.45 p = 0.247

Table 6.17: Haemoglobin Results Males : Individual Therapy Groups

Therapy Sequence	N	Baseline Hb (g/dl)	Mean Δ Hb (g/dl)	% Pts with Hb <13.5 g/dl at baseline	%Pts with Hb <13.5 g/dl at one year
Group A	8	14.9	-0.4	13	25
Group B	7	15.7	-0.8	0	14
Group C	6	14.8	-0.7	17	33
Group D	7	15.6	-0.9	29	14
Group E	4	15.2	0.05	0	0
Group F	6	15.5	-0.2	0	0
Total	38	15.3	-0.5	11	16

ANOVA: F = 0.68 p = 0.64

Table 6.18: Haemoglobin Results – Females : Primary Therapy Groups

Therapy Sequence	N	Baseline Hb (g/dl)	Mean Δ Hb (g/dl)	% Pts with Hb <11.5 g/dl at baseline	% Pts with Hb <11.5 g/dl at one year
Met Arm	7	14.5	-0.4	0	0
Ros Arm	8	14.0	-1.2	0	25
Glip Arm	7	13.4	-0.3	29	29
Total	22	13.9	-0.7	9	18

ANOVA: F = 1.93 p = 0.17

Table 6.19: Haemoglobin Results – Females : Individual Therapy Groups

Therapy Sequence	N	Baseline Hb (g/dl)	Mean Δ Hb (g/dl)	% Pts with Hb <11.5 g/dl at baseline	% Pts with Hb <11.5 g/dl at one year
A	3	14.4	-0.03	0	0
B	4	14.6	-0.6	0	0
C	2	14.9	-2.0	0	0
D	6	13.7	-1.0	0	33
E	3	14.0	-0.4	0	0
F	4	12.9	-0.3	50	50
Total	22	13.9	-0.7	9	18

ANOVA: F = 1.16 p = 0.37

Table 6.20: Alanine Aminotransferase (ALT) : Primary Therapy Groups

Therapy Sequence	N	Baseline ALT (iu/l)	Mean Δ ALT (iu/l)	% Pts with ALT > 53 iu/l at baseline	% Pts with ALT > 53 iu/l at one year
Met Arm	22	30.1	-1.8	14	5
Rosi Arm	21	33.7	-7.3	14	5
Glip Arm	17	32.6	-2.1	18	12
Total	60	32.1	-3.8	15	7

ANOVA: F = 1.31 p = 0.28

Table 6.21: Alanine Aminotransferase (ALT) : Individual Therapy Groups

Therapy Sequence	N	Baseline ALT (iu/l)	Mean Δ ALT (iu/l)	% Pts with ALT > 53 iu/l at baseline	% Pts with ALT > 53 iu/l at one year
Group A	11	26.6	1.1	0	0
Group B	11	33.6	-4.7	27	9
Group C	8	38.0	-11.3	25	0
Group D	13	31.0	-4.9	8	8
Group E	7	41.1	-7.7	29	14
Group F	10	26.6	1.9	10	10
Total	60	32.1	-3.8	15	7

ANOVA: F = 1.62 p = 0.17

Safety Criterion: ALT 53 = 1.5 x Upper Limit Normal Range

6.3.11: Adverse Events

A comprehensive list of adverse events experienced in the study is provided in Appendix 8. The number of adverse events experienced during the study was 63 and details are shown below. Most of the adverse events involved minor symptoms associated with concurrent illnesses. 31 were perceived to be related to study medication and these included predominantly gastrointestinal side effects of metformin, weight gain, ankle oedema and arthralgia with rosiglitazone. Others seemed to relate more to changes in glucose control and periods of hyperglycaemia with initial dose titrations (fatigue, leg ulcer, weakness, high blood glucose values). No serious adverse events were reported, but seven patients withdrew from the study as a result of their adverse events. The total duration of adverse events was 2926 days but only 13 work and non-work days were lost due to adverse events.

Table 6.22: Summary Adverse Events

Summary of Adverse Events	Number
Total number of adverse events in study	63
Number of adverse events perceived to be due to study medication	31
Number of study withdrawals arising from adverse events	7
Total number of serious adverse events in study	0
Total duration of adverse events (days)	2926
Total number of work and non-work days lost due to adverse events (days)	13

6.3.12. Patient support required during the study

24-hour telephone support was provided for patients and practice nurses by myself throughout the study. The table below shows the support required and provides an estimate of the backup required to extend this programme generally in primary care. Overall 266 contacts occurred outside of the study visits. The majority of these (128) were in the glipizide arm as a result of the increased proportion of patients allocated to insulin therapy in this group. 59 patient contacts occurred in the metformin arm and 79 in the rosiglitazone arm. The principal reason for telephone support was difficulties with insulin or advice relating to therapy doses, monitoring and lifestyle changes (shift work, business travel). Discussion of hypoglycaemia episodes and reiteration of rules relating to intercurrent illness episodes and study medication were also required occasionally.

Table 6.23: Number of telephone contacts outside of study visits:

Months	All Therapies	Metformin Arm	Rosiglitazone Arm	Glipizide Arm
0	4	0	4	0
1	16	6	6	4
2	22	2	11	9
3	34	5	9	20
4	30	5	6	19
5	35	13	8	14
6	37	11	15	11
7	28	7	0	21
8	15	2	9	4
9	13	3	3	7
10	8	1	3	4
11	17	4	5	8
12	7	0	0	7
Total	**266**	**59**	**79**	**128**

Chapter 7: Efficacy of the Programme

This chapter evaluates the efficacy of the protocol-led, target-driven programme of care in terms of overall HbA_{1c}, fasting and prandial glucose reduction, CVS risk factor modification, hypoglycaemia weight and markers of T2DM complications in the study. A comparison of the outcomes achieved in the glucose study with those achieved in non-recruited patients within standard care is provided. The efficacy of individual and primary therapy arms are discussed in chapter 8.

7.1. Glucose Data

A. HbA_{1c}

7.1.1: Mean HbA_{1c} reduction

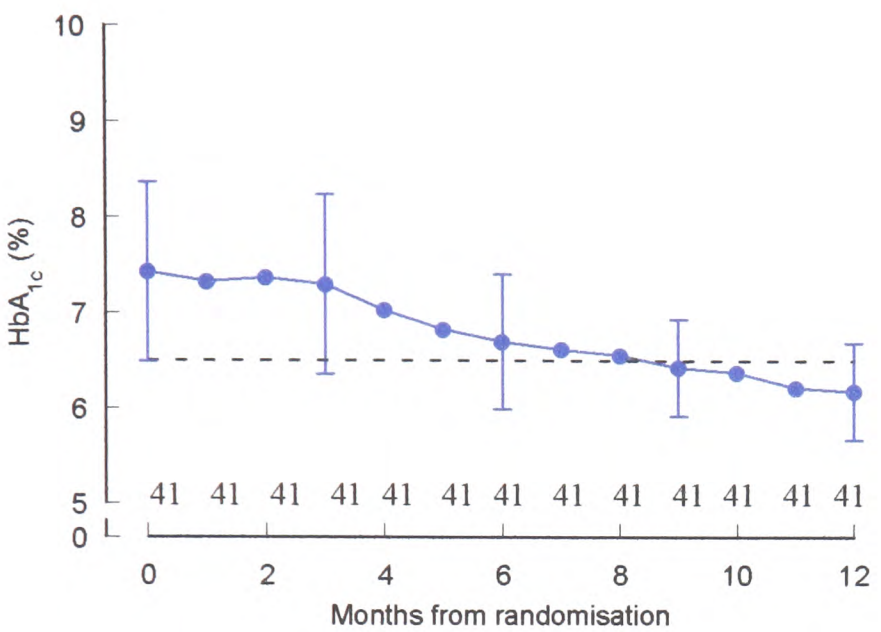
The overall mean HbA_{1c} reduction with cross-sectional and cohort analyses is shown in figure 7.1. A mean HbA_{1c} reduction of 0.8% was seen during the year with a reduction of 1.2% in protocol adherent patients. Overall mean HbA_{1c} decreased from 7.5% to 6.2% in protocol-adherent patients and 7.5% to 6.7% with ITT analyses. The decline in HbA_{1c} (0.11%) was slower in the first three months, increased to a maximum between months three and six (0.7%) and then subsequently declined at a steady rate of 0.25% every three months. The shape of cohort and cross-sectional graph data was similar and HbA_{1c} variability decreased with months from randomisation.

7.1.2: Proportion of patients achieving glucose targets

The proportion of patients achieving HbA_{1c} targets of 6.5% and 7% with cohort and cross-sectional analyses is shown in figure 7.2. Overall 95% of protocol-adherent patients (XS data) and 72% of all patients (ITT) achieved HbA_{1c} targets <7.0% at one year with 83% and 62% respectively achieved targets <6.5%.

Figure 7.1 : Mean ± SD HbA_{1c} (%) with months from randomisation: All Therapies

Cohort Data: $HbA_{1c} = 7.48 - 0.114$ Months $p < 0.0001$



Cross sectional data: $HbA_{1c} = 7.57 - 0.124$ Months Slope $p < 0.0001$

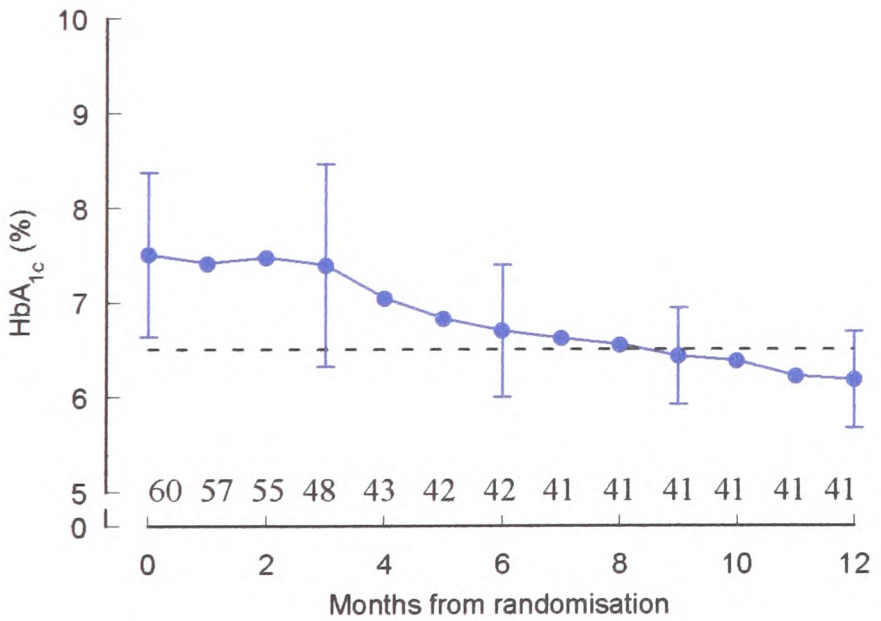
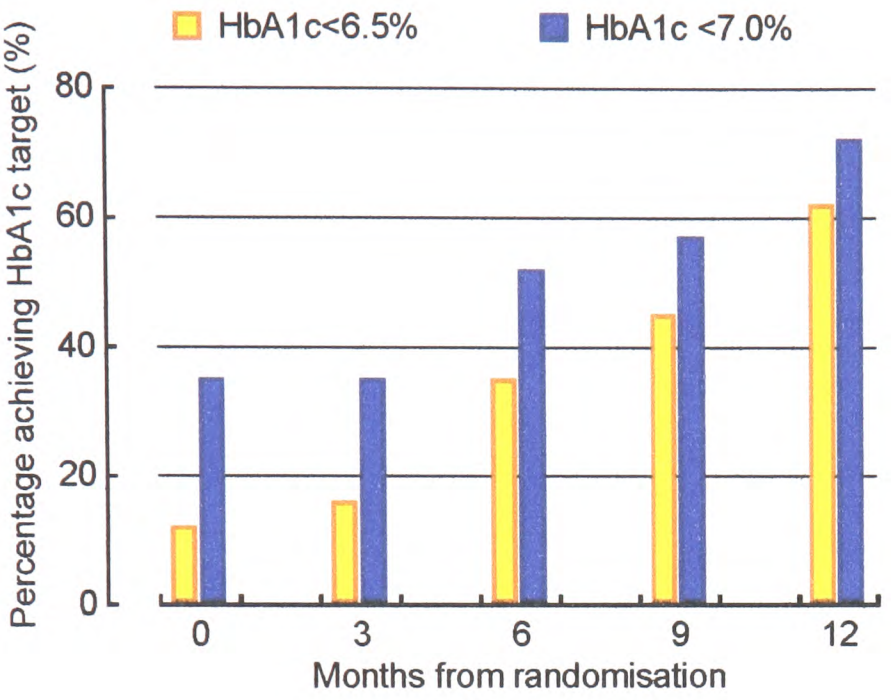


Figure 7.2: ITT percentage of patients achieving HbA_{1c} targets (N = 60)



B. Fasting plasma glucose (FPG)

7.1.3: Mean FPG with months from randomisation

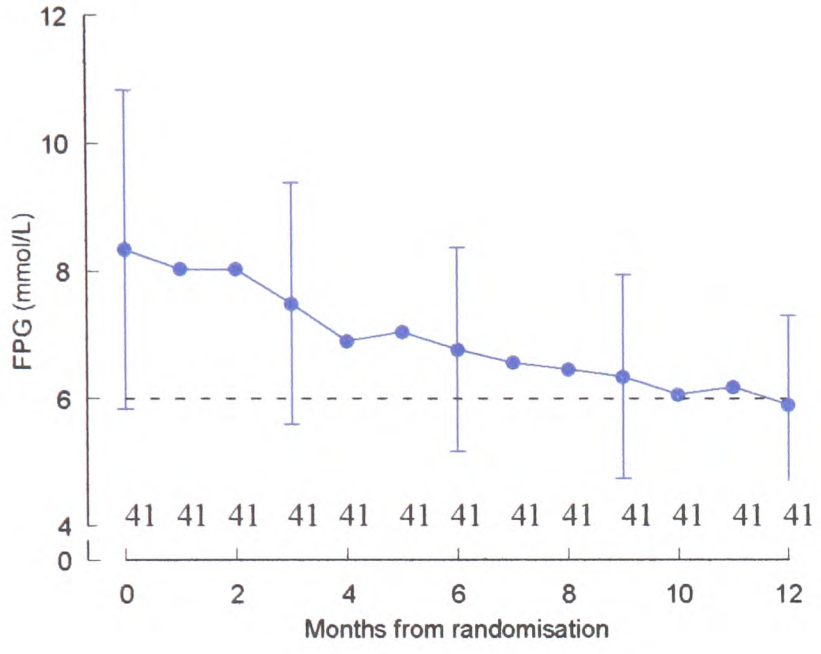
The overall mean FPG reduction in the study is shown in figure 7.3. A mean overall FPG reduction of −1.5mmol/L was seen during the year with a reduction of −2.4mmol/L in protocol adherent patients. Overall mean FPG decreased from 8.3mmol/L to 5.9mmol/L in protocol adherent patients and 8.1mmolL to 6.6mmol/L using ITT analyses. FPG changes mirrored those of HbA_{1c} but increased variability of the results was seen. The decline in FPG differed from HbA_{1c} with greater reductions in months 0-3 (0.8mmol/L) and 3-6 (0.8mmol/L) and subsequent slowing in months 6-9 and 9-12 (both 0.4mmol/L).

7.1.4: Proportion of patients achieving FPG targets

The proportion of patients achieving FPG targets is shown in figure 7.4. 61% of protocol-adherent patients (cohort data) and 45% of all patients (ITT) achieved FPG targets <6.0mmol/L at one year.

Figure 7.3 : Mean ± SD FPG (mmol/L) with months from randomisation:

Cohort Data FPG = 8.14 – 0.201 Months Slope $p < 0.001$



Cross-Sectional Data: FPG = 8.11 – 0.195 Months Slope $p < 0.001$

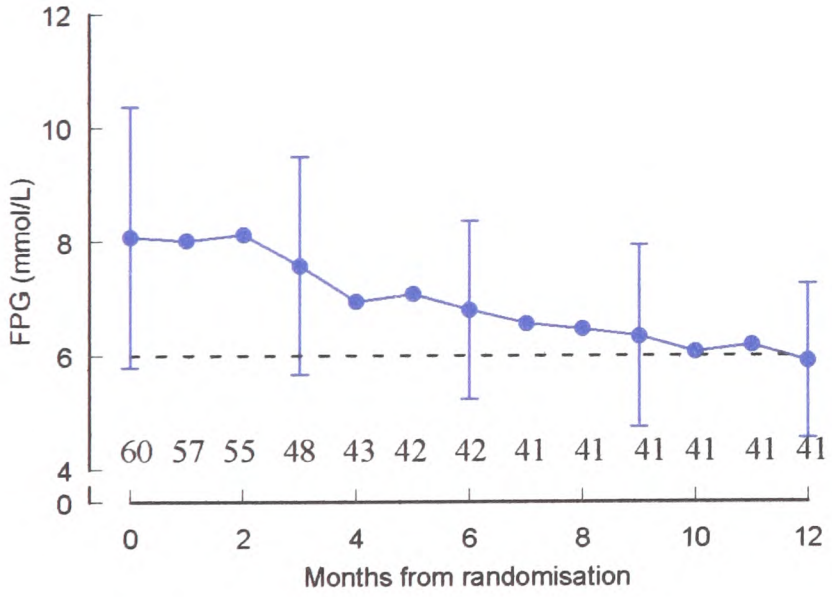
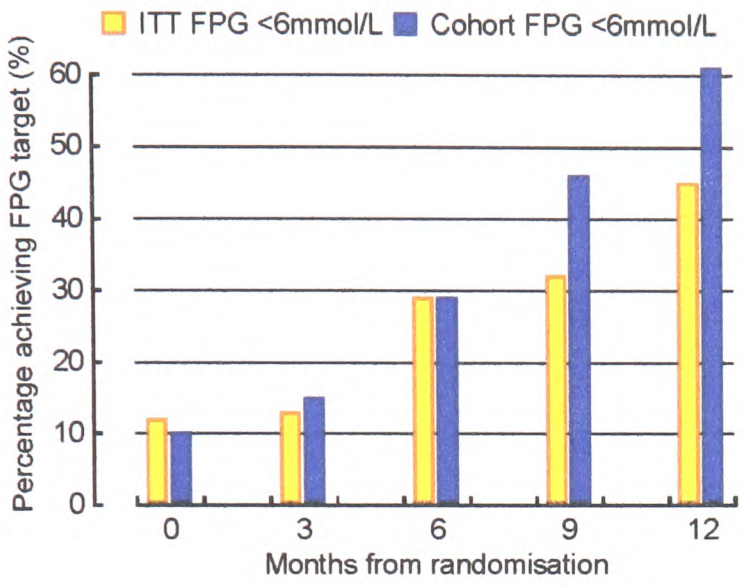


Figure 7.4: Proportion of patients achieving FPG targets (N = 60):



C. Post-prandial glucose (PPG)

2-hour PPG glucose results from home glucose monitoring records are shown below. Missing data was present predominantly in the XS dataset as a result of incomplete profiles or lack of monitoring in the month prior to withdrawal. Glucometer failure accounts for the missing data in one patient. Only complete glucose profiles were included in these analyses.

7.1.5: Mean PPG reduction with months from randomisation

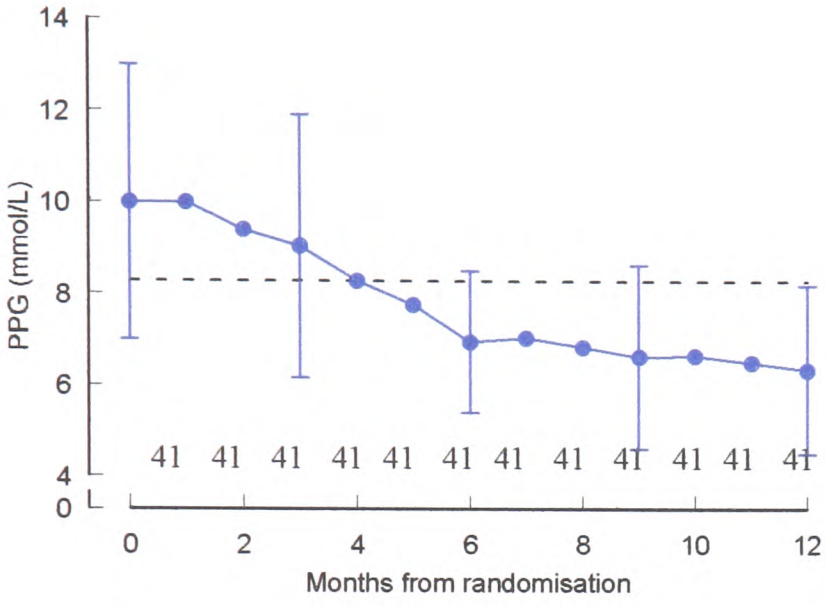
The overall mean PPG reduction in the study is shown in figure 7.5. A mean PPG reduction of 3.4 mmol/L from a baseline of 9.7 mmol/L with XS analyses and 3.7 mmol/L from a baseline of 10.0 mmol/L with cohort analyses was seen.

7.1.6: Proportion of patients achieving PPG targets

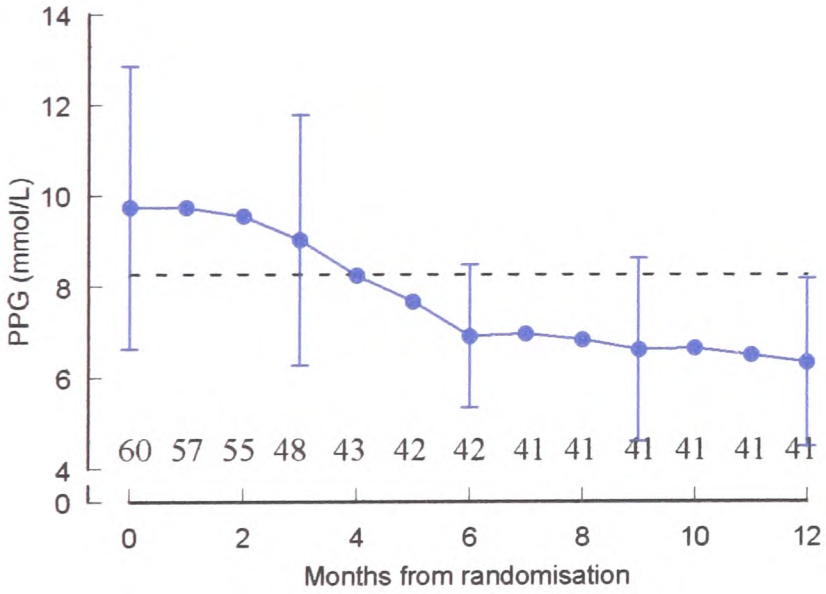
The proportion of patients achieving target PPG values <8.0 mmol/L rose from 0.29 to 0.82 over the year with cohort analyses.

Figure 7.5: Mean ± SD PPG reduction (mmol/L) with months from randomisation

Cohort Data PPG = 9.43 – 0.329 Months Slope $p < 0.001$



Cross-sectional data PPG = 9.36 – 0.322 Months Slope $p < 0.001$



7.1.7: Hypoglycaemia Episodes

98 episodes of mild (grade-1) hypoglycaemia symptoms were reported in the study but only 4 grade 2 episodes with significant symptoms confirmed by glucose tests, and one grade 3 episode requiring third person assistance occurred. No episodes of severe grade-4 hypoglycaemia requiring medical intervention occurred. The number of hypoglycaemia episodes peaked at 8 months with 17 Grade 1 and 2 Grade 2 episodes, and subsequently declined. The number of hypoglycaemia episodes was highest in the glipizide arm (45 Grade 1 and 1 Grade 2), moderate in the rosiglitazone arm (31 Grade 1, 3 Grade 2, 1 Grade 3) and lowest in the metformin groups (22 Grade 1). No significant differences between therapy arms were seen. A grade 3 hypoglycaemia episode with rosiglitazone and repaglinide therapies occurred at 4 months leading to patient withdrawal. The episode required only normal dietary glucose to correct but involved third person assistance as a result of the gym setting in which it occurred.

Table 7.1: Frequency and severity of hypoglycaemia episodes

Therapy	N	Grade 1	Grade 2	Grade 3	Grade 4
A	11	10	0	0	0
B	11	12	0	0	0
C	8	16	1	0	0
D	13	15	2	1	0
E	7	23	1	0	0
F	10	22	0	0	0
Total	**60**	**98**	**4**	**1**	**0**

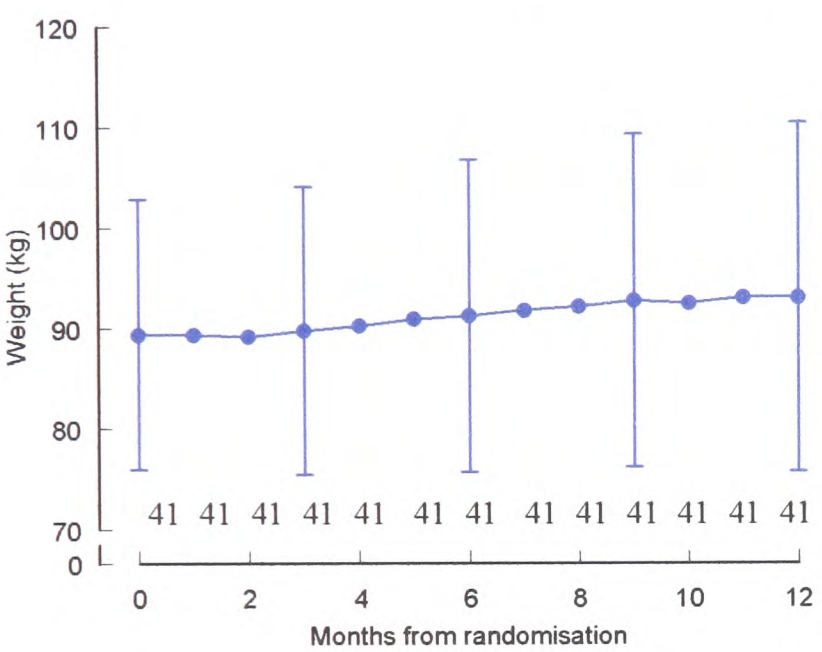
7.2. Body weight

Overall mean weight gain in the glucose study is shown in figure 7.6. No significant differences in baseline weight between therapy groups were seen as a result of BMI inclusion in the randomisation minimisation criteria. The mean weight at baseline was 89.0kg and 93.2kg at one year. A gradual increase in weight was observed through the study with no marked changes. The mean weight gain with cohort and ITT analyses respectively at one year was 3.8kg and 2.7kg. The regression equation for the weight plot in figure 7.6 shows significant weight gain during the course of the study ($p<0.001$). Cross-sectional and cohort analyses produced similar results.

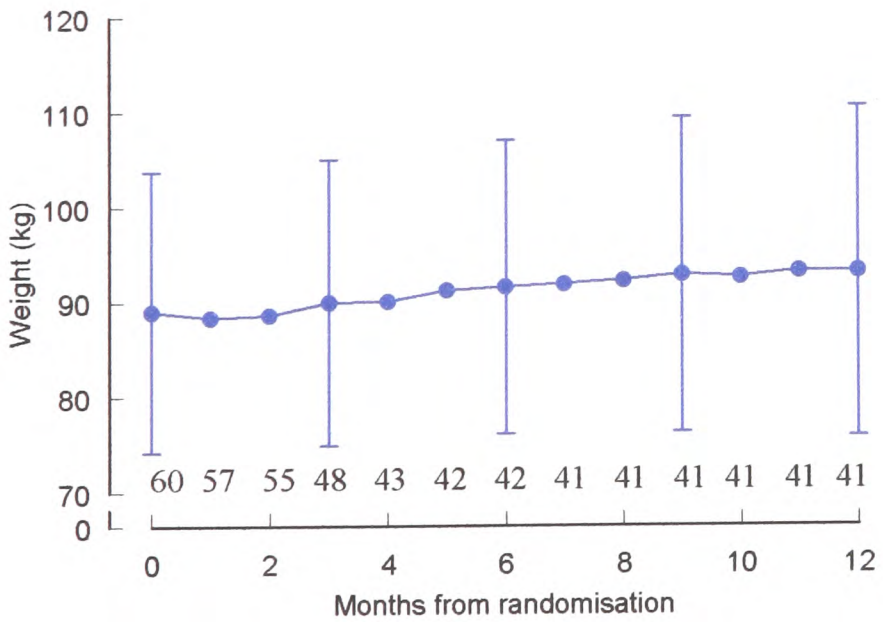
Significantly greater weight gain was seen in patients on insulin therapy than those treated with oral therapies. Mean weight gain for patients on humalog was 6.44 ± 8.07kg compared to those on OHA therapy 1.27 ± 4.37kg (p=0.002) and mean weight gain for patients treated with isophane therapy was 4.63 ± 7.55kg compared to 1.33 ± 4.30kg in patients on OHA alone (p=0.036).

Figure 7.6 : Overall mean ± SD weight (kg) with months from randomisation:

Cohort Data: Weight = 89 + 0.381 Months Slope p < 0.001



Cross-Sectional Data: Weight = 88.5 + 0.436 Months Slope p < 0.001



7.3. Blood Pressure Results

Systolic blood pressure changes in the study are shown in figure 7.7-7.10. An overall improvement was seen in SBP during the year with a reduction from 144 to 139 mmHg. No differences between cohort and XS data was seen. SBP significantly improved (p=0.05) in the cohort analyses but failed to reach significance in the XS analyses (p=0.186). ITT analyses revealed that 32% patients had SBP<135 mmHg at baseline and 42% at 12 months. SBP variability was large.

Similar results were seen for DBP as shown in figure 7.9-7.10. The overall mean reduction in DBP at one year with ITT analyses was 5 mmHg. Cohort analyses for protocol-adherent patients were similar with mean overall reductions of –7mmHg SBP and –6mmHg DBP. DBP variability was large and the regression equation for DBP shows once again a significant DBP improvement in cohort analyses (p=0.024) but borderline significant changes in the XS analyses (P=0.076). ITT analyses revealed that 40% patients had DBP <80 mmHg at baseline and 60% at 12 months.

Figure 7.7: Proportion of patients achieving SBP targets (N = 60):

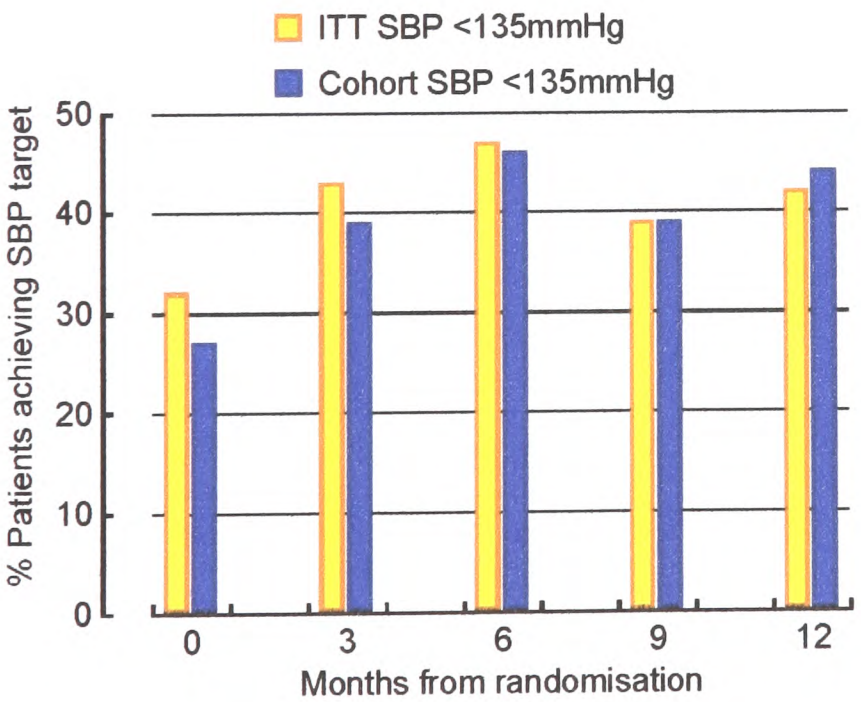
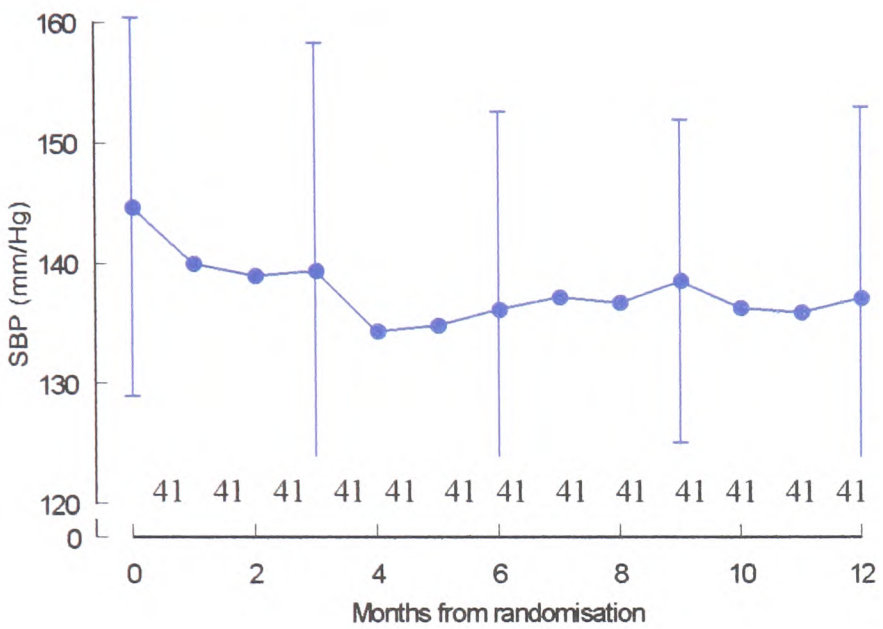


Figure 7.8: Overall mean ± SD SBP with months from randomisation

Cohort Data SBP = 140 – 0.380 Months Slope p = 0.05



Cross-Sectional Data SBP = 139 – 0.267 Months Slope p = 0.186

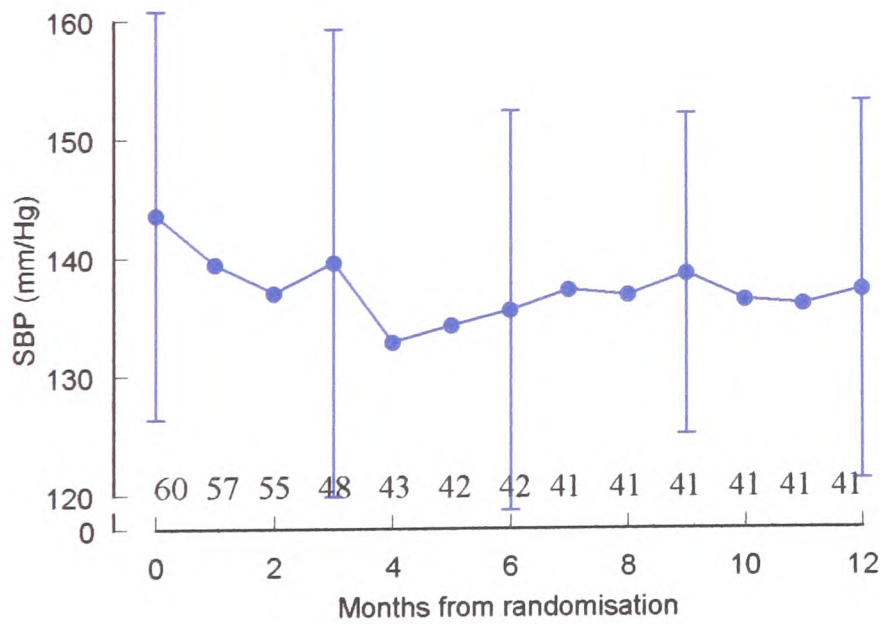
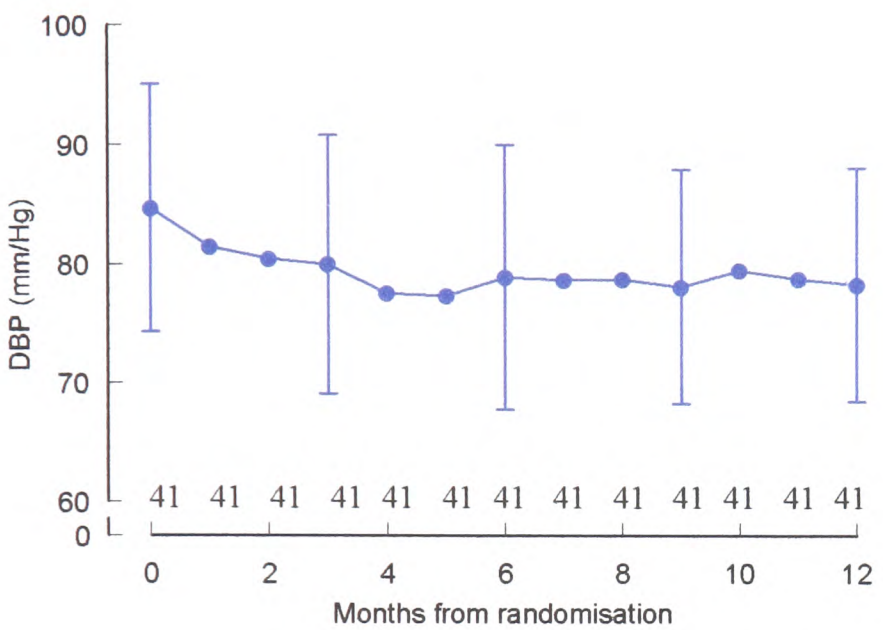


Figure 7.9: Overall mean ± SD DBP (mmHg) with months from randomisation

Cohort Data DBP = 81.3 –0.308 Months Slope p = 0.024



Cross-sectional data DBP = 80.6 – 0.235 Months Slope p = 0.076

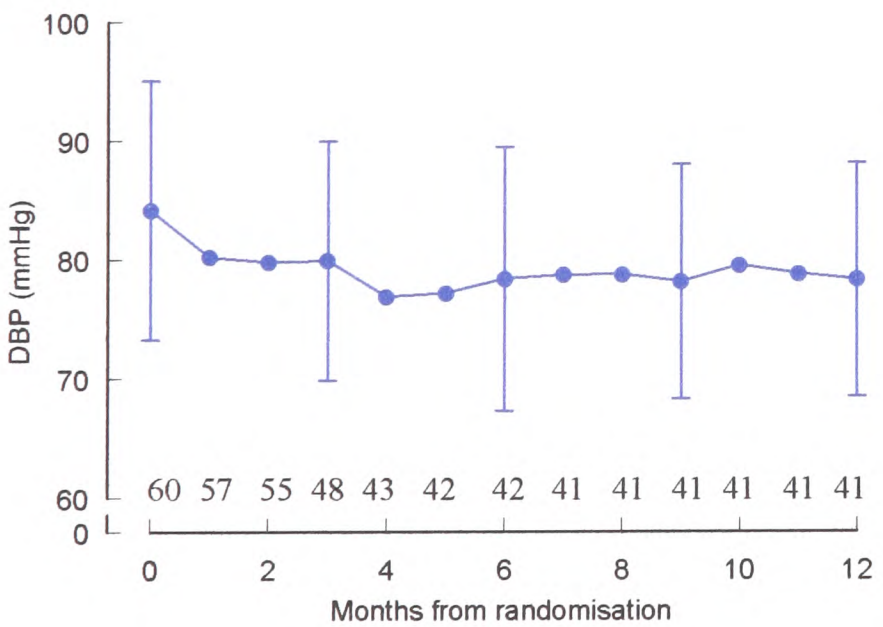
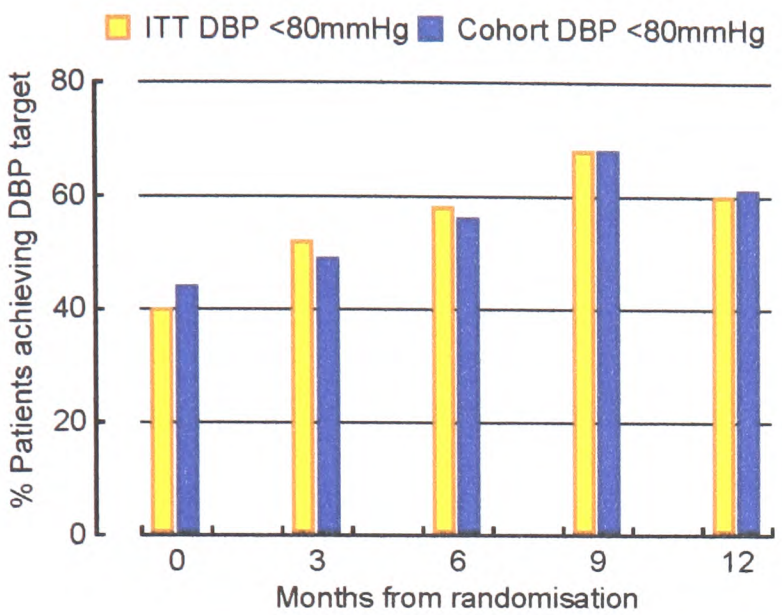


Figure 7.10: Proportion of patients achieving DBP targets (N=60):



7.4. Lipid Results

Lipid results are displayed in figure 7.11. A modest improvement in total cholesterol (p=0.189) was seen with 48% patients achieving targets at baseline compared to 63% at one year. Similar changes were observed in the LDL-cholesterol group with an overall increase from 57% to 63% achieving targets <3.4mmol/L at one year. An overall borderline significant improvement in HDL-cholesterol by 0.06 mmol/L was seen (p=0.066) with 68% of patients achieving targets at one year compared to 65% at baseline. Triglyceride improved significantly (p=0.001) in study patients during the year. The ITT proportion of patients achieving TG targets decreased from 62% to 58% and improved slightly in protocol-adherent patients (59% to 63%).

7.5. Cardiac Risk Results

7.5.1. Calculated CHD Risk

Cardiovascular risk, calculated at baseline and one year using the Joint Heart Guidelines is shown in table 7.2. CHD risk in glucose study patients reduced from 19.3% to 16.8% during the year, a mean change of 2.5% with both ITT and cohort analyses. A trend towards CVA risk reduction was also seen with –0.4% reduction in ITT and –0.8% in cohort analyses.

7.5.2. Biochemical Cardiovascular Risk Markers

Changes in conventional and novel CVD risk factors during the study are summarised in tables 7.2. All risk markers decreased over the year with the exception of Lp(a) which increased from 206 to 235. Paired t-test analyses revealed highly significant reductions in CHD risk (p=0.009), borderline significant changes in HDL-cholesterol (p=0.07) but no significant change in total-cholesterol (p=0.185) between baseline and one year. Lp(a) was significantly increased (p=0.001) but no significant changes in tPA (p=0.32), homocysteine (p=0.85), d-Dimer (p=0.54) or hsCRP (p=0.42).

Table 7.2: Change in cardiovascular risk in recruited patients over one year (n = 60):

	Baseline Data	One Year Data	P
Clinical			
Weight (kg)*	89.0 (14.8)	91.6 (17.6)	0.001
SBP (mmHg)*	144.7 (15.7)	137.3 (16.0)	0.042
DBP (mmHg)*	84.7 (10.4)	78.4 (9.9)	0.002
Smoking No/ex/cur (%)	30/53/17	30/53/17	1.00
CVS Risk Markers			
Total chol (mmol/L)*	5.1 (1.9)	5.0 (1.4)	0.185
HDL-chol (mmol/L)*	1.2 (0.4)	1.3 (0.3)	0.070
Lpa*	206.0 (314.0)	235.3 (316.1)	0.001
TPA*	11.5 (5.0)	10.8 (4.6)	0.32
HsCRP*	7.4 (10.8)	6.1 (9.2)	0.42
D-dimer*	110.6 (147.9)	98.9 (89.5)	0.54
Homocysteine*	16.5 (5.9)	16.4 (6.3)	0.85
Mean CHD Risk			
CHD Risk*	19.3 (8.1)	16.8 (7.8)	0.009
CVA Risk*	7.1 (4.5)	6.8 (4.3)	0.33

*Data are *mean (SD) or percentage (%)*

7.6: Comparison of glucose study outcomes with standard practice care

This section compares the clinical and biochemical outcomes achieved with the protocol-driven, treat-to-target approach with those attained in routine general practice over the same period. Tables 7.3-7.5 reports difference in outcomes achieved between patients who completed or withdrew from the glucose study, while tables 7.6-7.8 compare outcomes in the 60 recruited patients with those attained in the 285 non-recruited patients over the same time period.

7.6.1: Comparison of patients who completed and withdrew from the study

41 patients completed the study with 19 discontinuing treatment prior to one year. Patients who withdrew had a significantly greater T2DM duration than those who completed the study but no other significant baseline differences between the groups were apparent. No new complications occurred in patients who completed or withdrew from the study over the year.

At one year significant differences between the groups were seen with respect to HbA_{1c}, FPG and number of diabetes therapies. Patients who withdrew from the study had significantly higher HbA_{1c}, FPG and therapy use than those who completed the study. No HbA_{1c} change was seen in withdrawing patients during the year (7.7%) whereas in completers a decrease from 7.4 to 6.2% was observed. Similarly FPG increased in withdrawers (from 7.5mmol/L to 7.9mmol/L) but decreased (from 8.3mmol/L to 5.9mmol/L) in those completing the study. Significantly fewer therapies were taken by those withdrawing from the study with 95% on two therapies and 5% on monotherapy at one year, compared to 51% on 3 therapies, 34% on 2 and 15% on monotherapy in completers.

A non-significant trend towards lower weight gain and improved blood pressure was seen in completers. Weight increased by 3.8kg from 89.4 to 93.2kg in completers but remained stable in withdrawing patients at 88.2kg. Similarly SBP decreased by 7mmHg from 145 to 137mmHg and DBP by 6mmHg from 85 to 78mmHg in completers compared to an increase of 1mmHg to 142mmHg and decrease of 2mmHg to 82 mmHg in withdrawing patients. A non-significant trend towards increased triglyceride in withdrawing patients was seen with an increase of 0.6mmol/L to 2.0mmol/L compared to a stable 1.6mmol/L level in withdrawers. Total cholesterol was reduced by 0.1mmol/L in completers and 0.5mmol/L in withdrawers but LDL and HDL fractions remained relatively constant.

Table 7.3: Baseline characteristics of patients who completed and withdrew from the study

	Completed (n = 41)	Withdrew (n = 19)	P Value
Clinical			
Weight (kg)*	89.4 (13.5)	88.0 (17.6)	0.73
Systolic blood pressure (mmHg)*	144.7 (15.7)	141.2 (20.3)	0.47
Diastolic blood pressure (mmHg)*	84.7 (10.4)	83.1 (12.2)	0.59
Biochemical			
HbA_{1c} (%)*	7.4 (0.9)	7.7 (0.7)	0.30
FPG (mmol/L)*	8.3 (2.5)	7.5 (1.5)	0.20
Plasma Creatinine (μmol/L)‡	85 (70-103)	83 (67-102)	0.69
Alanine Transaminase (IU/L)‡	28 (18-44)	28 (16-51)	0.96
Total Cholesterol (mmol/L)*	5.1 (1.1)	5.3 (0.9)	0.49
LDL-Cholesterol (mmol/L)*	3.1 (1.0)	3.2 (0.7)	0.72
HDL-Cholesterol (mmol/L)*	1.2 (0.3)	1.3 (0.5)	0.73
Triglyceride (mmol/L) ‡	1.6 (0.8-3.2)	1.4 (0.7-2.8)	0.52
Urine albumin†	16 (6-38)	11 (6-31.5)	0.83
Diabetes Complications			
Retinopathy (%)	4 (9.8)	0 (0.0)	0.30
Neuropathy (%)	0 (0.0)	0 (0.0)	1.00
Ischaemic heart disease (%)	4 (9.8)	5 (26.3)	0.095
Peripheral vascular disease (%)	1 (2.4)	0 (0.0)	1.00
Nephropathy (%)	2 (4.9)	0 (0.0)	1.00
Medication			
Diabetes (%) diet / metformin / sulphonylurea	34/37/29	42/42/16	0.53

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

Table 7.4: Comparison of completed and withdrawal patient characteristics at 1 year

	Completed (n = 41)	Withdrew (n = 19)	P Value
Clinical			
Weight (kg)*	93.2 (17.4)	88.2 (18.0)	0.32
Systolic blood pressure (mmHg)*	137.3 (16.0)	141.9 (19.3)	0.37
Diastolic blood pressure (mmHg)*	78.4 (9.9)	81.5 (9.1)	0.24
Biochemical			
HbA_{1c} (%)*	6.2 (0.5)	7.7 (0.9)	0.0001
FPG (mmol/L)*	5.9 (1.4)	7.9 (1.6)	0.0001
Plasma Creatinine (μmol/L)‡	91.5 (17.6)	84.3 (16.1)	0.17
Alanine Transaminase (IU/L)‡	26.7 (12.9)	31.6 (18.5)	0.47
Total Cholesterol (mmol/L)*	5.0 (0.9)	4.8 (1.6)	0.52
LDL-Cholesterol (mmol/L)*	3.2 (0.7)	3.3 (0.7)	0.47
HDL-Cholesterol (mmol/L)*	1.3 (0.3)	1.3 (0.4)	0.45
Triglyceride (mmol/L) ‡	1.6 (0.9)	2.0 (1.8)	0.73
Urine albumin†	39.2 (84.8)	36.1 (77.0)	0.68
Diabetes Complications			
Retinopathy (%)	4 (9.8)	0 (0.0)	0.30
Neuropathy (%)	0 (0.0)	0 (0.0)	1.00
Ischaemic Heart Disease (%)	4 (9.8)	5 (26.3)	0.095
Peripheral Vascular Disease (%)	1 (2.4)	0 (0.0)	1.00
Nephropathy (%)	2 (4.9)	0 (0.0)	1.00
Medication			
Number of therapies (%) – 0/1/2/3	0/15/34/51	5/95/0/0	<0.0001

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

Table 7.5: Changes from baseline to one year by withdrawal status

	Δ Completed (n = 41)	Δ Withdrew (n = 19)	Δ Completed – Δ Withdrew
Clinical			
Weight (kg)*	3.8 (1.7, 5.9)	0.2 (-1.1, 1.5)	3.6 (1.1, 6.0)
Systolic blood pressure (mmHg)*	-7.4 (-13.0, -1.7)	0.7 (-7.3, 8.8)	-8.1 (-17.8, 1.5)
Diastolic blood pressure (mmHg)*	-6.3 (-10.0, -2.7)	-1.6 (-6.8, 3.7)	-4.7 (-11.0, 1.5)
Biochemical			
HbA_{1c} (%)*	-1.2 (-1.5, -0.9)	0.0 (-0.3, 0.4)	-1.2 (-1.7, -0.8)
FPG (mmol/L)*	-2.4 (-3.3, -1.6)	0.4 (-0.6, 1.5)	-2.0 (-4.2, -1.5)
Plasma Creatinine (μmol/L)*	5.1 (2.6, 7.5)	-0.4 (-4.1, 3.4)	5.5 (1.0, 9.8)
Alanine Transaminase (IU/L)*	-4.3 (-8.4, -0.3)	-2.6 (-8.2, 2.9)	-1.7 (-8.4, 5.0)
Total Cholesterol (mmol/L)*	-0.1 (-0.4, 0.3)	-0.5 (-1.2, 0.1)	0.4 (-0.2, 1.2)
Triglyceride (mmol/L) *	-0.5 (-1.1, 0.0)	0.2 (-0.1, 0.5)	-0.7 (-1.3, -0.1)
Urine albumin*	-6.3 (-22.7, 10.1)	1.8 (-19.0, 22.6)	-1.9 (-34.0, 17.7)
Diabetes Complications			
Retinopathy (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Neuropathy (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Ischaemic Heart Disease (%)	1.0 (0.0, 2.0)	0.0 (0.0, 0.0)	1.0 (0.0, 2.0)
Peripheral Vascular Disease (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Nephropathy (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

*All data are % or *mean differences with 95% confidence interval*

7.6.2: Comparison of recruited and non-recruited patients

Baseline characteristics of recruited and non-recruited patients were similar with only duration of T2DM, smoking status, fasting glucose, total-cholesterol and smoking status differing significantly between groups. T2DM duration was shorter in recruited patients at three versus four years and significantly lower total-cholesterol (5.1 versus 5.5mmol/L) and FPG (8.1 vs 9.6mmol/L) were seen. Recruited patients were more likely to be ex or never smokers than non-recruited patients.

At one year significant differences between recruited and non-recruited patients were seen in HbA_{1c}, FPG, TG and medication use. HbA_{1c} decreased from 7.5% to 6.7% in recruited patients but was unchanged at 7.8% in non-recruited groups. Equally FPG decreased from 8.1 to 6.6mmol/L in recruited patients but increased from 9.6 to 10.1mmol/L in non-recruited groups. Triglyceride decreased from 2.0 to 1.7mmol/L in recruited patients but remained constant at 2.2mmol/L in non-recruited groups. The number of therapies taken by recruited patients was significantly higher than non-recruited groups at one year with 100% on combination therapy compared to 0% in non-recruited patients. Increased retinopathy, neuropathy, nephropathy and IHD were seen in non-recruited patients during the year but no new microvascular or macrovascular complications were observed in study patients.

Table 7.6 : Baseline Characteristics of Recruited and Non Recruited Patients

	Recruited (n = 60)	Non-Recruited (n = 285)	P Value
Demographic			
Gender (M/F)	39/21	176/109	0.64
Age (years)*	60.9 (8.2)	60.3 (9.6)	0.61
Clinical			
Weight (kg)*	89.0 (14.8)	87.8 (18.7)	0.58
Body mass index (kg/m^2)*	30.5 (4.9)	30.3 (5.7)	0.68
Systolic blood pressure (mmHg)*	144 (17.2)	147 (20.7)	0.21
Diastolic blood pressure (mmHg)*	84 (10.9)	83 (10.8)	0.52
Diabetes duration (years)†	3.0 (1.0-5.0)	4.0 (2.0-7.0)	0.021
Documented hypertension (%)	50.0	42.8	0.31
Documented hyperlipidaemia (%)	25.0	13.3	0.020
Documented cardiovascular disease (%)	15.0	9.2	0.016
Tobacco smoking (%) nev/ex/cur/unknown	30/53/17/0	40/15/20/25	<0.0001
Excessive alcohol intake (%)	0.0	9.0	1.00
Biochemical			
HbA_{1c} (%)*	7.5 (0.9)	7.8 (1.7)	0.12
Fasting Plasma Glucose (mmol/L)*	8.1 (2.9)	9.6 (3.8)	<0.0001
Plasma Creatinine (μmol/L)‡	84.3 (69.3-102.5)	89.4 (69.5-115)	0.31
Alanine Transaminase (IU/L)‡	28.2 (17.3-45.9)	--	--
Total Cholesterol (mmol/L)*	5.1 (1.1)	5.5 (1.1)	0.038
LDL-Cholesterol (mmol/L)*	3.2 (0.9)	--	--
HDL-Cholesterol (mmol/L)*	1.2 (0.4)	--	--
Triglyceride (mmol/L)‡	1.5 (0.8-3.0)	2.2 (1.2-4.0)	0.15
Urine albumin†	15 (6-38)	--	--
Documented Existing Complications			
Retinopathy (%)	4 (6.7)	23 (8.1)	1.00
Neuropathy (%)	0 (0.0)	4 (1.4)	1.00
Ischaemic Heart Disease (%)	9 (15.0)	26 (9.1)	0.21
Peripheral Vascular Disease (%)	1 (1.7)	3 (1.1)	0.54
Nephropathy (%)	2 (3.3)	7 (2.5)	0.66
Medication			
Diabetes (%) diet /metformin /sulphonylurea/combn	37/25/38/0	33/26/37/4	0.91

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

Table 7.7: Comparison of Recruited and Non-Recruited Patients at 1 Year

	Recruited (n = 60)	Non-Recruited (n = 285)	P Value
Demographic			
Gender (M/F)	39/21	176/109	0.64
Age (years)*	61.9 (8.2)	61.3 (9.6)	0.61
Clinical			
Weight (kg)*	91.7 (17.2)	87.7 (19.4)	0.14
Body mass index (kg/m^2)*	31.1 (5.2)	30.4 (5.9)	0.21
Systolic blood pressure (mmHg)*	138.8 (17.1)	141.3 (18.2)	0.31
Diastolic blood pressure (mmHg)*	79.4 (9.7)	80.1 (9.9)	0.58
Diabetes duration (years)†	4.0 (2.0-6.0)	5.0 (3.0-8.0)	0.21
Documented hypertension (%)	32 (53.3)	160 (56.1)	0.69
Documented hyperlipidaemia (%)	15 (25.0)	38 (13.3)	0.023
Documented cardiovascular disease (%)	9 (15.0)	34 (11.9)	0.51
Tobacco smoking (%) nev/ex/cur/unknown	30/60/10/0	40/15/20/25	<0.0001
Biochemical			
HbA_{1c} (%)*	6.7 (0.9)	7.8 (1.7)	<0.0001
Fasting Plasma Glucose (mmol/L)*	6.6 (1.6)	10.1 (4.2)	<0.0001
Plasma Creatinine (μmol/L)‡	87.6 (72-106)	85.8 (61-120)	0.54
Total Cholesterol (mmol/L)*	4.8 (1.1)	5.3 (1.1)	0.023
Triglyceride (mmol/L)‡	1.4 (0.8-2.6)	2.2 (1.2-3.9)	<0.0001
Documented Existing Complications			
Retinopathy (%)	4 (6.7)	29 (10.2)	0.48
Neuropathy (%)	0 (0.0)	8 (2.8)	0.36
Ischaemic Heart Disease (%)	9 (15.0)	34 (11.9)	0.51
Peripheral Vascular Disease (%)	1 (1.7)	3 (1.1)	0.54
Nephropathy (%)	2 (3.3)	9 (3.2)	1.00
Medication			
Diabetes (%) diet /metformin /sulphonylurea /combn	0/0/0/100	34/38/28/0	<0.0001

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

Table 7.8: Changes between baseline and one year by recruitment status

	Δ Recruited (n = 60)	Δ Non-Recruited (n = 285)	Δ Recruited – Δ Non-Recruited
Clinical			
Weight (kg)*	2.7 (1.1, 4.2)	-0.1 (-0.6, 0.5)	2.8 (1.1, 4.3)
SBP (mmHg)*	-4.8 (-9.5, -0.2)	-5.0 (-7.7, -2.3)	0.2 (-5.2, 5.5)
DBP (mmHg)*	-4.8 (-7.8, -1.8)	-2.1 (-3.7, -0.5)	-2.7 (-6.1, 0.7)
Biochemical			
HbA_{1c} (%)*	-0.8 (-1.1,-0.5)	0.0 (-0.2, 0.2)	-0.8 (-1.3, -0.5)
FPG (mmol/L)*	-1.5 (-2.3, -0.79)	0.5 (-0.1, 1.2)	-2.0 (-3.0, -1.0)
Total Chol (mmol/L)*	-0.3 (-0.6, 0.1)	-0.1 (-0.2, 0.0)	-0.2 (-0.6, 0.2)
Existing Complications			
Retinopathy (%)**	0.0 (0.0, 0.0)	2.1 (-3.0, 7.0)	2.1 (-3.0, 7.0)
Neuropathy (%)**	0.0 (0.0, 0.0)	1.4 (-1.0, 4.0)	1.4 (-1.0, 4.0)
IHD (%)**	0.0 (0.0, 0.0)	2.8 (-2.2, 7.8)	2.8 (-2.2, 7.8)
PVD (%)**	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Nephropathy (%)**	0.0 (0.0, 0.0)	0.7 (-2.0, 3.4)	0.7 (-2.0, 3.4)

*All data are *mean differences or **% with 95% confidence intervals*

Chapter 8: Comparison of Therapeutic Sequences

8.1: Therapy Use

No significant differences between the mean number of therapies used within each algorithm were seen. The mean number was 0.7 at baseline in the metformin arm, 0.6 in the rosiglitazone group and 0.8 in the glipizide arm. By 6 months the mean number of therapies taken were 1.9, 2.2 and 2.1 respectively. The mean number of therapies continued to increase after this time in the rosiglitazone and glipizide groups to 2.5 respectively by 12 months but stayed relatively more constant at 2.0 in the metformin arm. The mean number of therapies taken in individual treatment sequences A-F at one year was 1.7, 2.3, 2.8, 2.3, 3.0 and 2.3 respectively.

Figures 8.1 illustrates the number of therapies taken with each algorithm. Within the metformin arm the number of patients on diet therapy alone decreases sharply from 32% pre-study to 5% at 2 months and 0% at 3 months. The number of patients on monotherapy declines from 95% at 1 month to 61% at 3 months and remains constant at 21% from 7 months. No patients in the metformin arm take 3 therapies until 6 months when the proportion is constant at 22%. No patients in this therapy arm ever take 4 therapies.

Within the rosiglitazone arm the numbers of patients on diet and monotherapy decline more sharply. 43% of patients are on diet alone pre-study onset and 57% are on monotherapy. By 4 months no patients are on diet alone and only 8% remain on monotherapy. From 10 months all patients are taking either 2 or 3 therapies. The proportion on each remains constant at 46% and 54% until study closeout. No patients in this therapy arm ever take 4 therapies.

A different trend is seen again in the glipizide arm. The proportion of patients on diet declines sharply from 24% to 0% at 1 month and the proportion on monotherapy decreases from 100% at 1 month to 21% at 6 months and then remains constant. 60% of patients within this group take 2 therapies at 3 months but 0% by 11 months. The proportion of patients on 3 therapies increases from 7% at 3 months to 79% at 12 months. 7% of patients take 4 therapies between months 4 and 5.

The proportion of patients on maximal OHA therapy differs between the primary therapy groups. 64% of patients are on maximal metformin doses at one year compared to 100% in the rosiglitazone and 86% in the glipizide arms. The increase to maximal therapy is most rapid in the rosiglitazone arm as a result of the forced titration used with the delayed onset of glucose lowering. Doses of

glipizide are increased next rapidly and the increase in metformin doses is slowest. This most likely reflects the difference in glucose values at baseline between the subgroups and the forced titration method used in the rosiglitazone groups as a result of its delayed onset of action.

No patients in the study receive maximal doses of prandial therapies at one year although acarbose is used in maximal dose in 22% of patients at 4 and 33% at 5 months. The decline in use of maximal doses of acarbose after this point reflects its poor tolerability in patients. No patients in the study ever reach maximal doses of repaglinide but it is used in submaximal doses in 50% of patients in repaglinide therapy sequences at 3 months and 100% patients at 5 months

Table 8.1: Mean number of therapies taken with months from randomisation

Time (months)	N	All Therapies	Metformin Arm	Rosiglitazone Arm	Glipizide Arm
0	60	0.7	0.7	0.6	0.8
3	48	1.6	1.4	1.6	1.7
6	42	2.1	1.9	2.2	2.1
9	41	2.2	2.0	2.3	2.4
12	41	2.4	2.0	2.5	2.5

Insulin Use

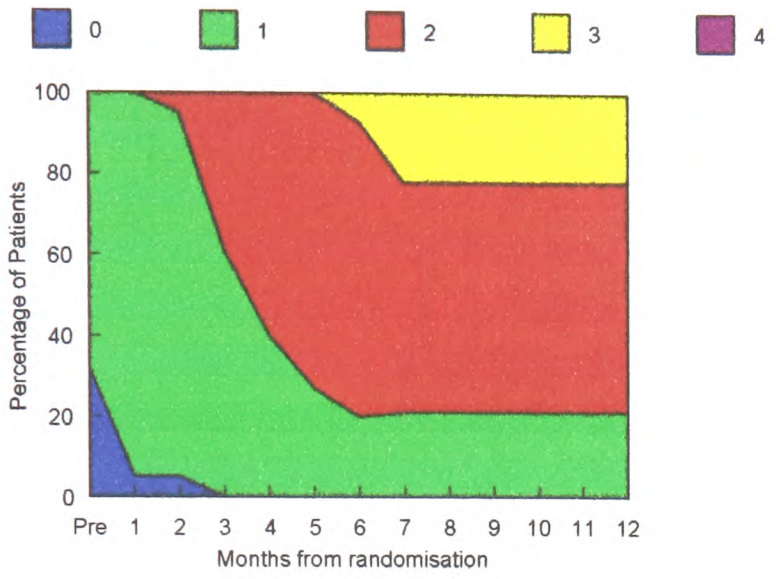
24 patients were successfully commenced on isophane and 16 on humalog; 5 in the metformin, 8 in the rosiglitazone and 11 in the glipizide arm. 16 were commenced on humalog, 12 by randomisation and 4 for additional prandial control; 2 in the metformin, 5 in the rosiglitazone and 9 (64%) in the glipizide arm. Significantly more patients commenced isophane and humalog in the glipizide arm than the metformin or rosiglitazone groups.

Table 8.2: Number (ITT%) of patients on insulin:

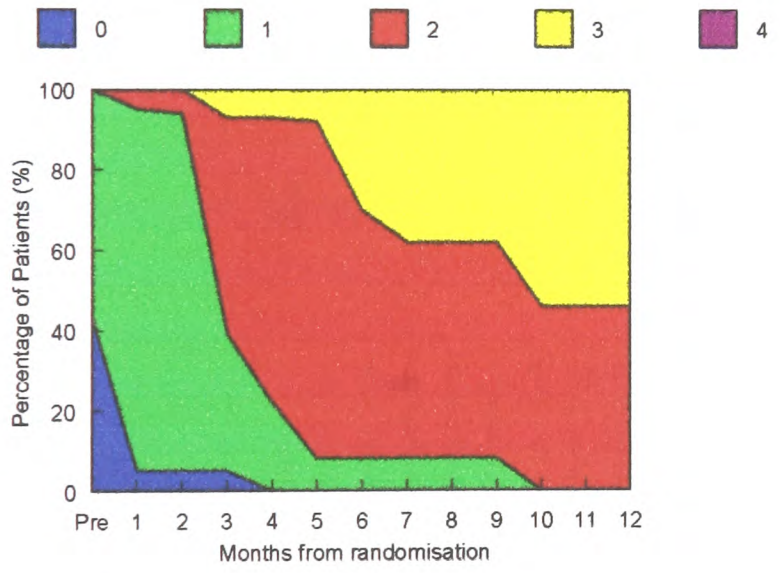
Time (Mo)	Isophane			Humalog		
	Met Arm	Rosi Arm	Glip Arm	Met Arm	Rosi Arm	Glip Arm
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	0 (0%)	1 (5%)	2 (12%)	1 (5%)	5 (24%)	3 (18%)
6	3 (14%)	4 (19%)	4 (24%)	3 (14%)	5 (24%)	9 (53%)
9	5 (23%)	5 (24%)	10 (59%)	2 (9%)	5 (24%)	9 (53%)
12	5 (23%)	8 (38%)	11 (65%)	2 (9%)	5 (24%)	9 (53%)

Figure 8.1: Mean number of therapies taken by primary therapy group:

Metformin Arm:



Rosiglitazone Arm:



Glipizide Arm:

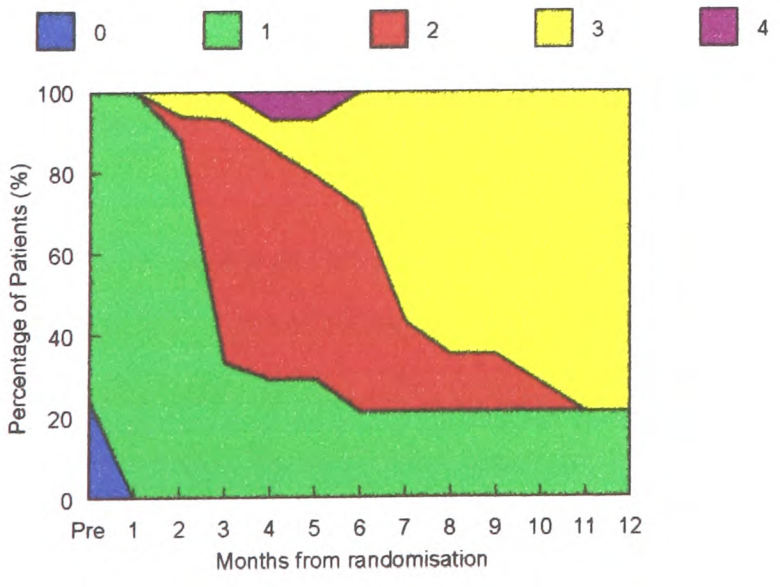


Figure 8.2 : Isophane use by primary therapy arm: **Chi Square:** X = 7.09 p = 0.029

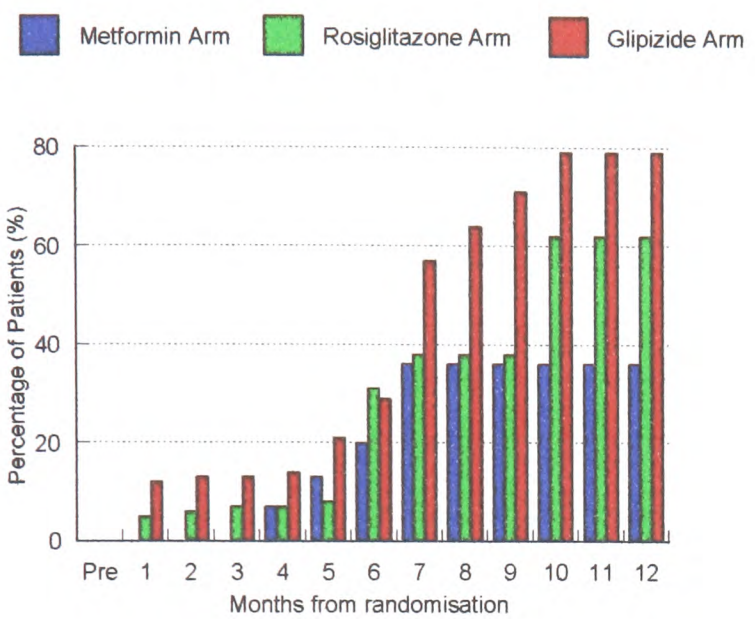
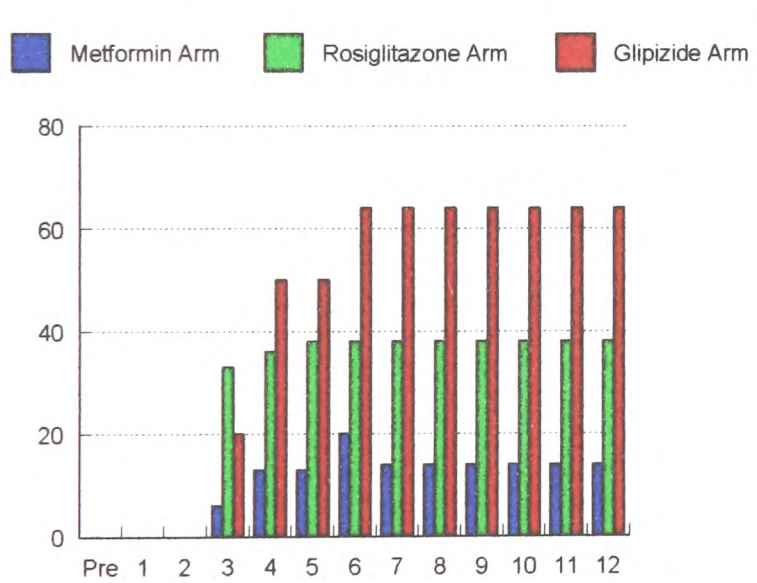


Figure 8.3: Humalog use by primary therapy arm: **Chi Square:** X = 9.56 p = 0.008



8.2: Adherence

Dietary adherence was comparable in all therapy algorithms at baseline but adherence declined more in the glipizide arm with months from randomisation. 53% glipizide patients were always adherent, 35% usually adherent and 12% sometimes adherent to diet at baseline compared to 18%, 59% and 24% at one year. The respective figures for rosiglitazone were 33%, 67% at baseline and 29%, 52% and 19% at one year. Within the metformin arm full diet adherence increased from 23% at baseline

to 27% at one year with usual adherence decreasing from 77% and 64%, and some adherence from 0% to 9%.

Adherence to high fibre foods was less in metformin groups at baseline and declined most markedly in this arm during the study. The respective data for metformin, glipizide and rosiglitazone groups from baseline to one year were 18% to 9%, 24% to 14% and 24% to 24%. The percentage of patients who never consumed high fat or sweet foods increased from 14% to 23% with metformin and 14% to 24% with rosiglitazone but remained constant in glipizide groups at 18%.

Exercise adherence was greatest in the rosiglitazone arm with 33% patients always adherent at baseline and one year and never adherent patients decreasing from 14% to 5%. Exercise adherence increased in metformin therapy groups (from 18% to 45%) during the year and decreased in glipizide groups (from 18% to 12%).

Adherence to basal therapy was highest in the metformin arm at baseline with 95% of patients reporting full adherence compared to 70% in rosiglitazone and 71% in glipizide arms. By one year the metformin groups had the worst adherence with only 50% always adherent to basal therapy compared to 62% in rosiglitazone and 71% in glipizide groups. Adherence to prandial therapy was highest in the glipizide sequences at 64% compared to 55% in rosiglitazone and 47% in metformin arms. 2% of all patients, 6% of metformin and 5% of rosiglitazone treated patients reported total non-adherence to prandial therapies. 51% of metformin patients reported full adherence to isophane compared to 50% of rosiglitazone and 71% of glipizide patients. Adherence to basal, prandial and insulin therapy with actual therapy analyses in valid cases was 88%, 88% and 92% at one year.

8.3 HbA_{1c} Reduction

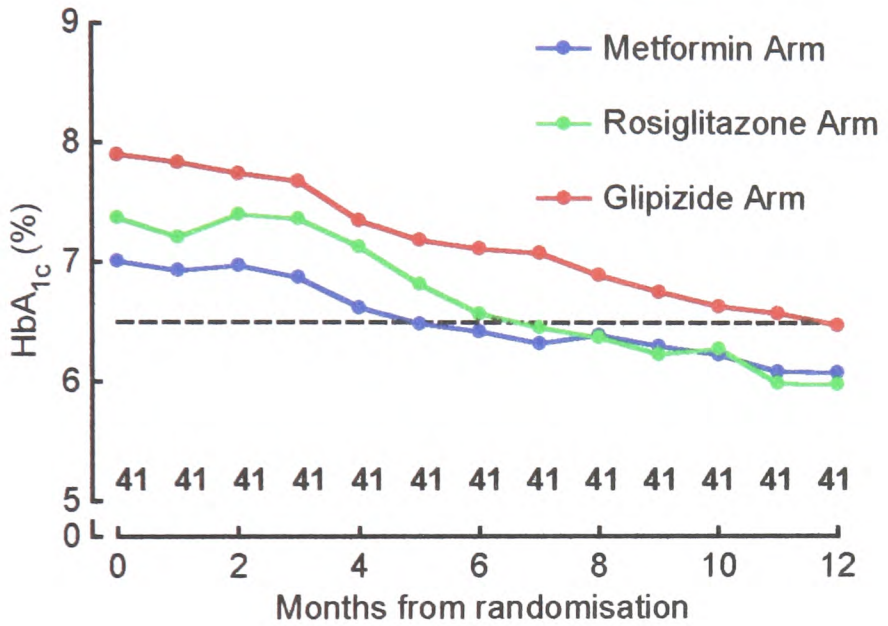
The mean HbA_{1c} reduction for primary therapy groups is shown in table 8.3, figures 8.4 and 8.7 and the effect of individual therapy sequences is shown in table 8.4. A significant baseline difference in HbA_{1c} was seen in the study with lower values in the metformin arm (7.1%) and higher in the rosiglitazone (7.6%) and glipizide (8.0%) arms. Despite this difference no significant differences in glucose lowering between therapy arms were seen at one year (ANOVA $F=1.07$ $p=0.385$ IAUC $F=0.62$ $p=0.543$). Whilst all statistical tests used are shown the IAUC provides the most valid data.

HbA_{1c} reduction was initially delayed in the rosiglitazone arm with 3 month values exceeding baseline levels but subsequent catch-up was observed. Mean HbA_{1c} values were reduced from 7.1% to 6.2% in the metformin arm, from 7.6% to 6.0% in the rosiglitazone arm and from 8.0% to 6.5%

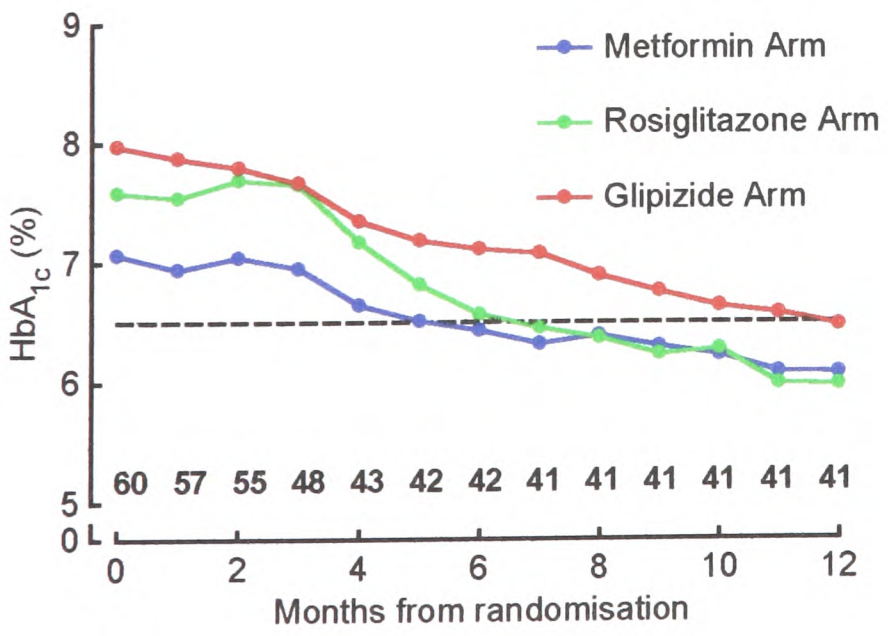
in the glipizide arm. Similar reductions in HbA_{1c} were seen with the individual therapy sequences. Mean HbA_{1c} was reduced from 7.1% to 6.2% with sequence A, 7.0% to 5.9% with B, 7.6% to 6.1% with C, 7.6% to 5.9% with D, 8.5% to 6.5% with E and 7.6% to 6.5% with F. No significant differences in HbA_{1c} reduction were seen between sequences (IAUC F=0.62 p=0.543).

Figure 8.4 : Mean HbA_{1c} with months from randomisation: Primary therapy sequences

Cohort Data



Cross Sectional Data



No significant differences between primary therapies were seen. 86% of protocol-adherent and 64% of all patients in the metformin therapy arm achieved HbA_{1c} <6.5% compared with 100% and 87% in the rosiglitazone and 64% and 53% in the glipizide arm. The respective figures for the HbA_{1c} <7.0% target were 100% and 77% for metformin, 100% and 67% for rosiglitazone and 86% and 71% for glipizide therapy arms. Chi square analyses are shown.

No significant differences between individual algorithms were seen. 71% of protocol-adherent patients and 55% of all patients achieved HbA_{1c} <6.5% with sequence A, 100% and 73% with B, 100% and 75% with C, 100% and 62% with D, 60% and 43% with E and 67% and 56% with F. The respective figures for the HbA_{1c} <7.0% target were 100% and 73% for sequence A, 100% and 82% for B, 100% and 75% for C, 100% and 62% for D, 100% and 71% for E and 78% and 70% for F. Chi square analyses are shown.

The proportion of patients achieving both targets increased with months from randomisation in all arms. A comparison of the relative proportion of patients attaining HbA_{1c} targets at quarterly intervals in each of the primary therapy arms reveals significant differences. The proportion of patients achieving targets is highest in the metformin arm and lowest in the glipizide arm in the first 8 months. At 3 months 43% of metformin patients have achieved HbA_{1c}<6.5% compared to 31% of rosiglitazone and 21% of glipizide patients. At 6 months the respective figures are 71%, 62% and 14% whilst at 9 months 71% of the metformin patients, 85% of rosiglitazone and 43% of glipizide groups have reached target. Similar trends are seen in the proportion of patients achieving HbA_{1c} targets <7.0% and in individual sequences. The proportion of patients attaining HbA_{1c} targets is significantly lower in sequence E for the first ten months than in other groups

Figure 8.5: Proportion of patients achieving HbA_{1c} targets < 6.5%

Chi Square = 0.81 p = 0.67

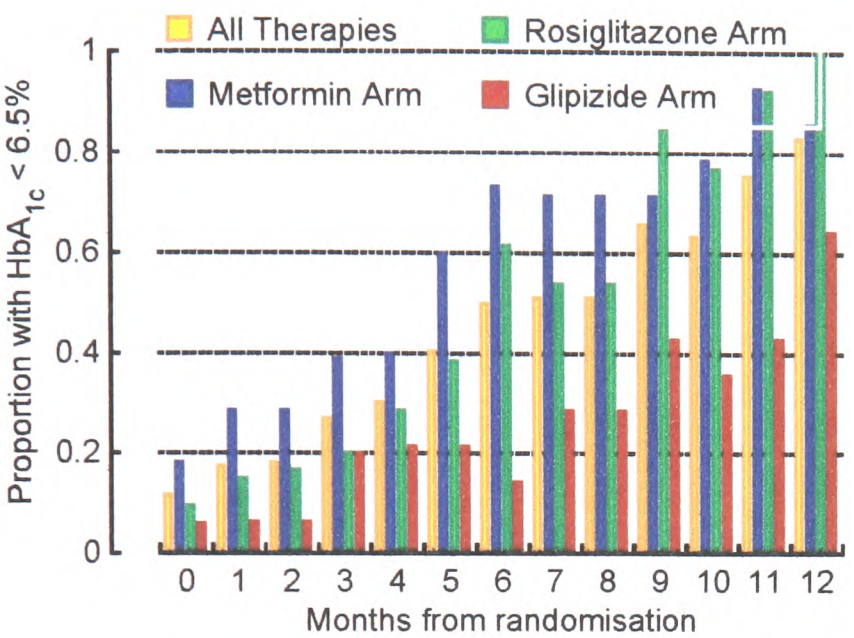
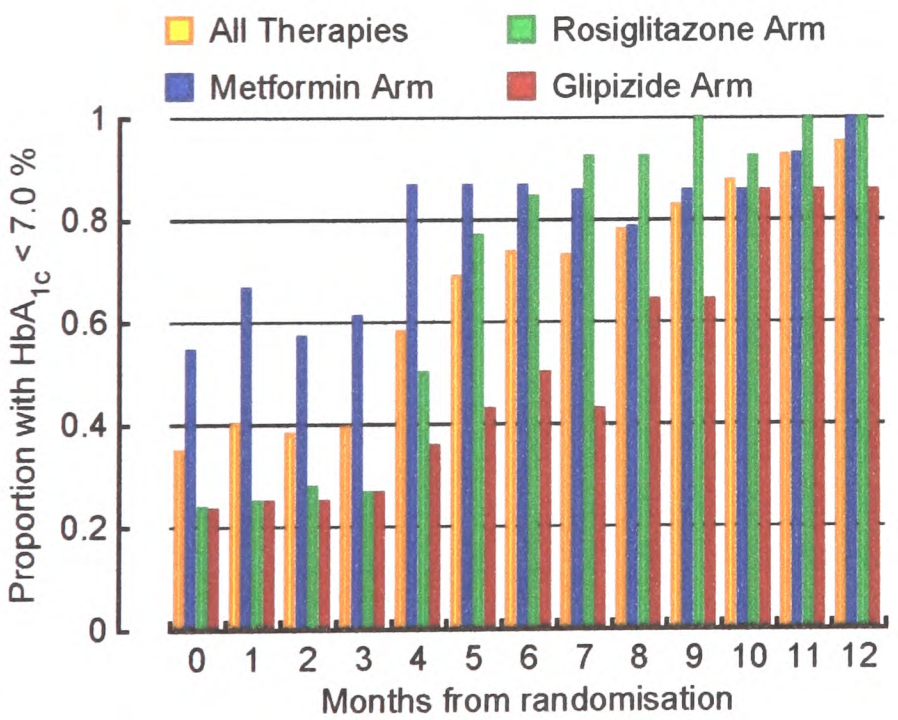


Figure 8.6: Proportion of patients achieving HbA_{1c} targets < 7.0%

Chi Square = 0.61 p = 0.74



Summary HbA_{1c} Results

Table 8.3 : Summary HbA_{1c} Results for primary therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline HbA_{1c}	Mean Δ HbA_{1c}	% HbA_{1c} < 6.5%	% HbA_{1c} < 7.0%
Metformin Arm	22	7.1 (0.7)	-0.5 (0.8)	64	77
Rosiglitazone Arm	21	7.6 (0.8)	-0.9 (1.1)	67	67
Glipizide Arm	17	8.0 (0.9)	-1.2 (1.1)	53	71
Total	60	7.5 (0.9)	-0.8 (1.0)	62	72

ANOVA : F = 2.30 p = 0.109 **ANCOVA** : Baseline p = 0.009 Therapy p = 0.875

Cohort Analysis:

Therapy Sequence	N	Baseline HbA_{1c}	Mean Δ HbA_{1c}	% HbA_{1c} < 6.5%	% HbA_{1c} < 7.0%
Metformin Arm	14	7.0	-0.9	86	100
Rosiglitazone Arm	13	7.4	-1.4	100	100
Glipizide Arm	14	7.9	-1.4	64	86
Total	41	7.4	-1.2	83	95

ANOVA : F = 1.21 p = 0.308 **ANCOVA** : Baseline p = 0.341 Therapy p = 0.061

Table 8.4 : Summary HbA_{1c} Results for individual therapy groups

Intention to Treat Analysis:

Therapy Sequence	N	Baseline HbA_{1c}	Mean Δ HbA_{1c}	% HbA_{1c} < 6.5%	% HbA_{1c} < 7.0%
A. metformin ± humalog	11	7.1 (0.7)	-0.5 (0.9)	55	73
B. metformin ± repaglinide	11	7.0 (0.6)	-0.6 (0.7)	73	82
C. rosiglitazone ± humalog	8	7.6 (0.8)	-0.9 (1.2)	75	75
D. rosiglitazone ± repaglinide	13	7.6 (0.9)	-0.9 (1.2)	62	62
E. glipizide ± humalog	7	8.5 (0.9)	-1.5 (1.4)	43	71
F. glipizide ± acarbose	10	7.6 (0.8)	-1.0 (0.9)	56	70
Total	60	7.5 (0.9)	-0.8 (1.1)	62	72

ANOVA: F = 1.07 p = 0.385 **ANCOVA**: Baseline p = 0.018 Therapy p = 0.990

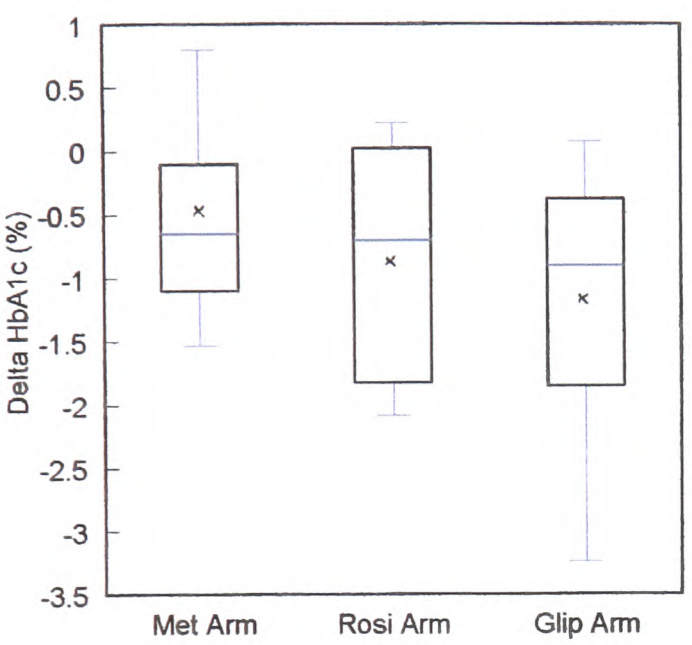
Cohort Analysis:

Therapy Sequence	N	Baseline HbA_{1c}	*Mean Δ HbA_{1c}	% †HbA_{1c} < 6.5%	% ‡HbA_{1c} < 7.0%
A. metformin ± humalog	7	7.1 (0.9)	-0.9 (0.7)	71	100
B. metformin ± repaglinide	7	6.9 (0.4)	-1.0 (0.4)	100	100
C. rosiglitazone ± humalog	6	7.4 (0.8)	-1.4 (0.9)	100	100
D.rosiglitazone ± repaglinide	7	7.3 (1.1)	-1.4 (1.2)	100	100
E. glipizide ± humalog	5	8.6 (1.0)	-2.1 (1.1)	60	100
F. glipizide ± acarbose	9	7.5 (0.8)	-1.0 (1.0)	67	78
Total	41	7.4 (0.9)	-1.2 (0.9)	83	95

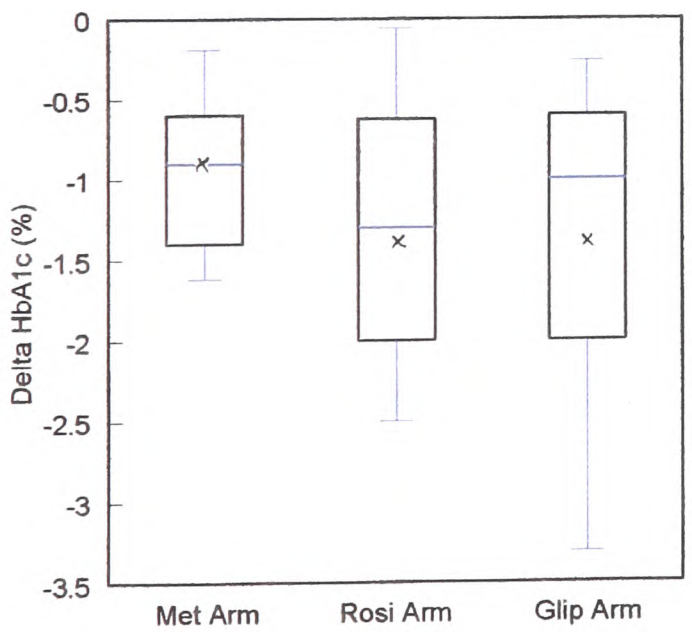
ANOVA : F = 1.36 p = 0.26 **ANCOVA** : Baseline p = 0.356 Therapy p = 0.222

Figure 8.7 : A Box Whisker Plot of ΔHbA_{1c} by Primary Therapy Group:

Intention to Treat Data:



Cohort Data:



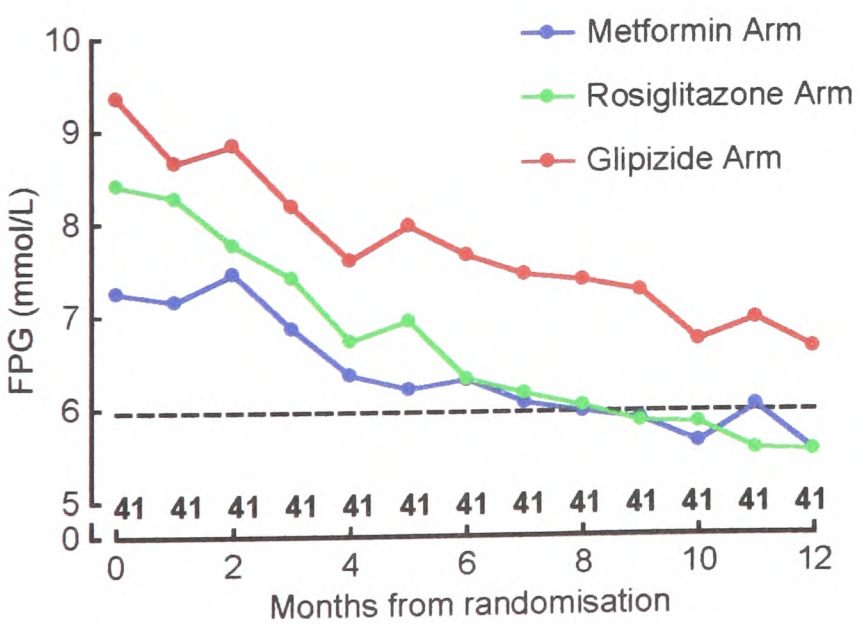
8.4: Fasting Plasma Glucose (FPG) Reduction

The mean FPG reduction for primary therapy groups is shown in figure 8.8 and table 8.5 and the effect of individual therapy sequences in table 8.6. A significant baseline difference in FPG was seen in the study with lower values in the metformin arm (6.9mmol/L) and higher in glipizide (9.4mmol/L) and rosiglitazone (8.3 mmol) arms. Despite this difference no significant differences in glucose lowering between therapy arms were seen at one year (ANOVA F=2.53 p=0.089).

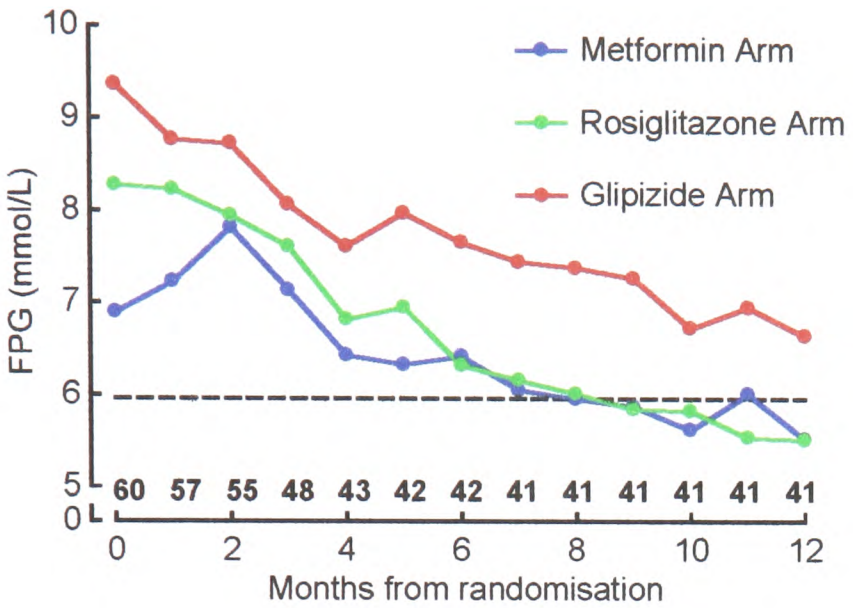
The delay in HbA_{1c} lowering seen with rosiglitazone was not mirrored by FPG changes. Mean FPG fell by 1mmol/L in the rosiglitazone arm over the first three months compared to a decrease of 1.2mmol/L in the glipizide and 0.8mmol/L in the metformin arm. Mean FPG values were reduced from 6.9mmol/L to 6.4mmol/L in the metformin arm, from 8.3 to 6.5mmol/L in the rosiglitazone arm and from 9.4 to 6.9 mmol/L in the glipizide arm.

Similar reductions in FPG were seen with the individual therapy sequences. Mean FPG was reduced from 7.2 to 6.1mmol/L with sequence A, 6.8 to 6.7mmol/L with B, 9.3 to 6.5mmol/L with C, 7.7 to 6.5 mmol/L with D, 10.7 to 7.1mmol/L with E and 8.1 to 6.8mmol/L with F. No significant differences in FPG were seen between therapy sequences (F=1.89 p=0.111).

Figure 8.8 : Mean FPG (mmol/L) with months from randomisation by primary therapies: Cohort Data



Cross sectional data:



The proportion of patients achieving FPG targets <6.0mmol/L with months from randomisation is shown in tables 8.5-8.6. Data is provided for primary therapy arms and for individual algorithms and both cohort and XS analyses are shown. Primary therapy data is provided in table 8.5 and individual algorithm data in table 8.6. Summary ITT and XS data at one year are shown.

No significant differences between primary therapy arms were seen (F=2.53 p=0.089). 64% of protocol-adherent patients and 50% of all patients in the metformin arm achieved FPG<6.0mmol/L compared with 85% and 52% in the rosiglitazone and 36% and 29% in the glipizide arm.

Similarly no significant differences between individual algorithms were seen (F=1.89 p=0.111). 71% of protocol-adherent patients and 55% of all patients achieved FPG <6.0mol/L with sequence A, 57% and 45% with B, 83% and 63% with C, 86% and 46% with D, 20% and 14% with E and 44% and 40% with F.

Summary FPG Results

Table 8.5: Summary FPG Results for primary therapy groups

Intention to Treat Analysis:

Therapy Sequence	N	Baseline FPG (mmol/l)	Mean Δ FPG (mmol/l)	% Pts with FPG < 6.0 mmol/l
Metformin Arm	22	6.9 (1.4)	-0.5 (2.6)	50
Rosiglitazone Arm	21	8.3 (1.7)	-1.8 (2.3)	52
Glipizide Arm	17	9.4 (3.1)	-2.5 (3.7)	29
Total	60	8.1 (2.3)	-1.5 (2.9)	45

ANOVA: F = 2.53 p = 0.089 **ANCOVA**: Baseline p = 0.552 Therapy p = 0.568

Cohort Analysis:

Therapy Sequence	N	Baseline FPG	Mean Δ FPG	% Pts with FPG < 6.0 mmol/l
Metformin Arm	14	7.3 (1.3)	-1.7 (1.7)	64
Rosiglitazone Arm	13	8.4 (2.1)	-2.9 (2.0)	85
Glipizide Arm	14	9.4 (3.4)	-2.7 (4.0)	36
Total	41	8.3 (2.5)	-2.4 (2.8)	61

ANOVA: F = 0.70 p = 0.501 **ANCOVA**: Baseline p = 0.899 Therapy p = 0.048

Table 8.6 : Summary FPG results for individual therapy groups

Intention to Treat Analysis:

Therapy Sequence	N	Baseline FPG	Mean Δ FPG	% Pts with FPG < 6.0 mmol/l
A. metformin ± humalog	11	7.0 (1.3)	-1.1 (2.5)	55
B. metformin ± repaglinide	11	6.8 (1.5)	0.1 (2.7)	45
C. rosiglitazone ± humalog	8	9.3 (2.3)	-2.8 (3.3)	63
D. rosiglitazone ± repaglinide	13	7.7 (0.8)	-1.2 (1.1)	46
E. glipizide ± humalog	7	10.7 (3.5)	-3.6 (3.9)	14
F. glipizide ± acarbose	10	8.5 (2.6)	-1.7 (3.5)	40
Total	60	8.1 (2.3)	-1.5 (2.9)	45

ANOVA: F = 1.89 p = 0.111 **ANCOVA**: Baseline p = 0.458 Therapy p = 0.640

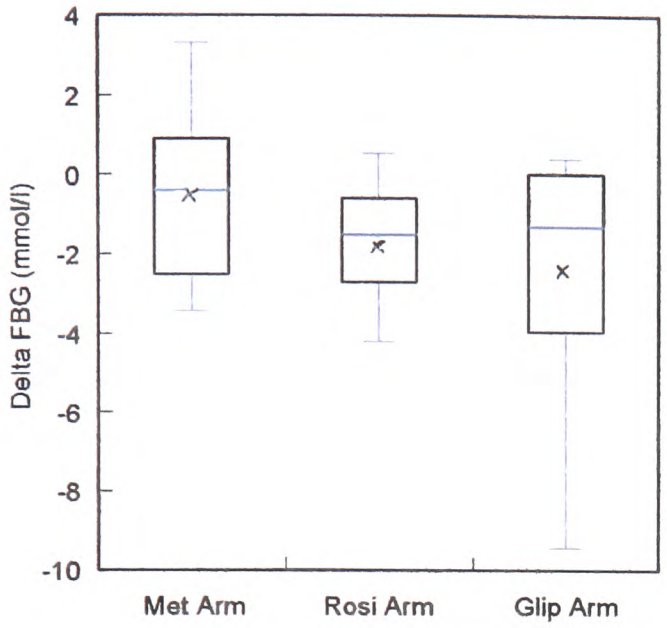
Cohort Analysis:

Therapy Sequence	N	Baseline FPG	Mean Δ FPG	% Pts with FPG < 6.0mmol/l
A. metformin ± humalog	7	7.2 (1.4)	-2.1 (2.0)	71
B. metformin ± repaglinide	7	7.3 (1.4)	-1.4 (1.5)	57
C. rosiglitazone ± humalog	6	9.6 (2.6)	-4.1 (2.5)	83
D. rosiglitazone ± repaglinide	7	7.4 (0.7)	-1.9 (0.7)	86
E. glipizide ± humalog	5	11.1 (4.1)	-4.6 (4.2)	20
F. glipizide ± acarbose	9	8.4 (2.8)	-1.7 (3.7)	44
Total	41	8.3 (2.5)	-2.4 (2.8)	61

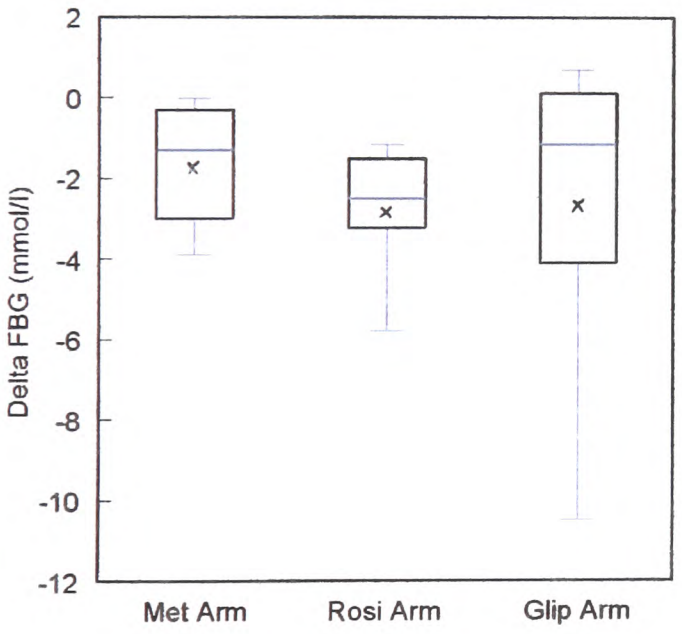
ANOVA: F = 1.52 p = 0.208 **ANCOVA**: Baseline p = 0.940 Therapy p = 0.213

Figure 8.9: A Box Whisker Plot of ΔFPG (mmol/l) with primary therapies

Intention to Treat Data:



Cohort Data

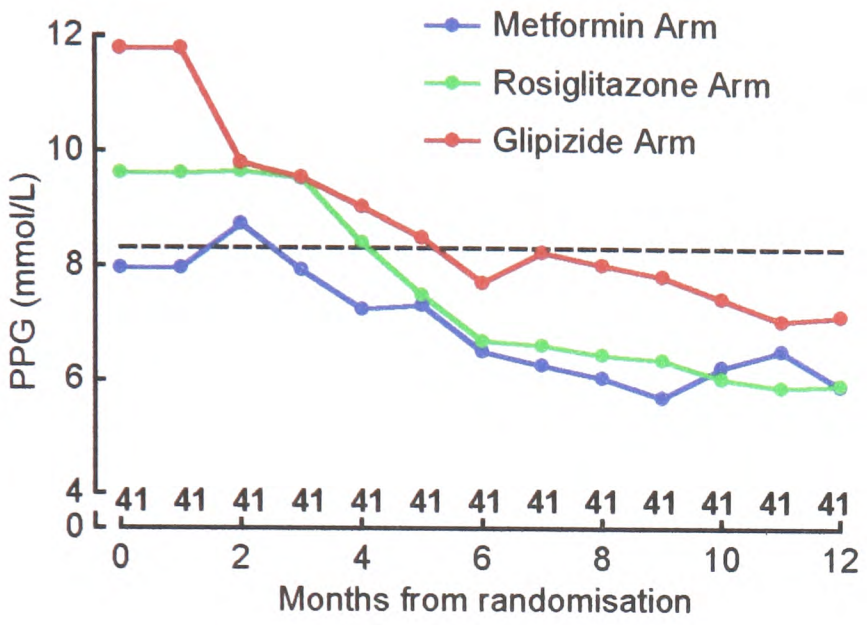


8.5: Post-Prandial Glucose Reduction

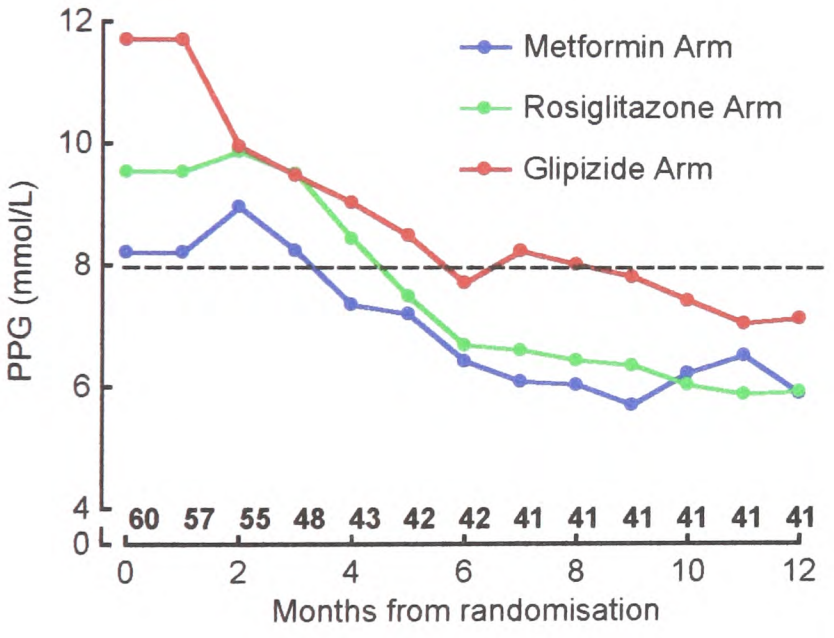
No significant difference between therapy groups was seen. The proportion of patients attaining PPG targets increased from 0.44 to 0.90 in the metformin arm, from 0.28 to 0.88 with rosiglitazone sequences and from 0.14 to 0.70 in the glipizide therapy groups.

Figure 8.10: Mean PPG reduction (mmol/L) with primary therapies

Cohort Data



Cross sectional data



Summary PPG Results

Table 8.7: Summary PPG results for primary therapy groups

Cohort Analysis:

Therapy Sequence	N	Baseline PPG	Mean Δ PPG	% Pts with PPG < 8.0 mmol/l
Metformin Arm	14	8.0 (2.2)	-2.1	90
Rosiglitazone Arm	13	9.6 (2.3)	-3.7	88
Glipizide Arm	14	11.8 (3.4)	-4.7	70
Total	41	10.0 (3.2)	-3.7	82

ANOVA: F = 0.84 p = 0.44

Table 8.8 : Summary PPG results for individual therapy groups

Cohort Analysis:

Therapy Sequence	N	Baseline PPG	Mean Δ PPG	% Pts with PPG < 8.0 mmol/l
A. metformin ± humalog	7	8.9 (2.1)	-2.9	93
B. metformin ± repaglinide	7	7.1 (2.0)	-1.3	88
C. rosiglitazone ± humalog	6	10.4 (2.8)	-4.1	83
D. rosiglitazone ± repaglinide	7	8.9 (1.4)	-3.2	92
E. glipizide ± humalog	5	13.6 (3.0)	-6.1	61
F. glipizide ± acarbose	9	10.7 (3.2)	-3.8	75
Total	41	10.0 (3.2)	-3.7	70

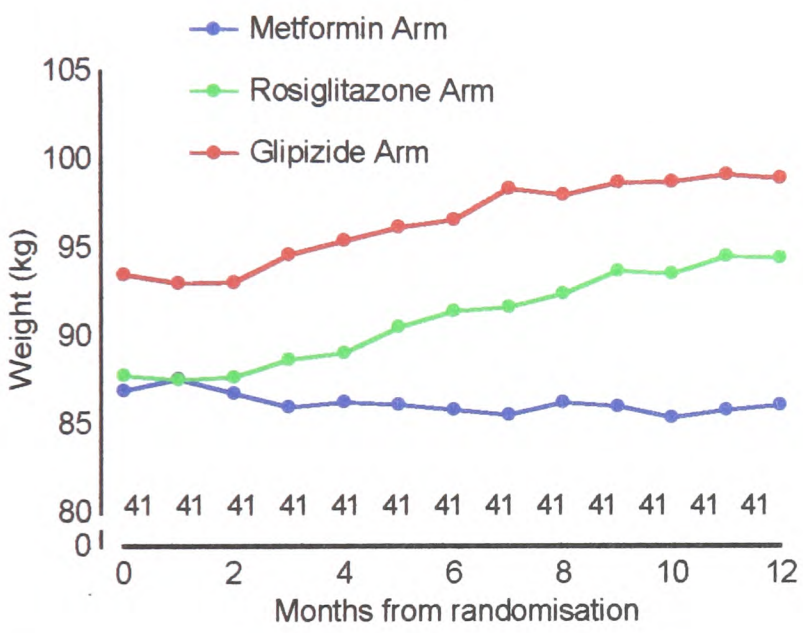
ANOVA: F = 0.60 p = 0.70

8.6: Weight Change

Significantly greater weight gain was observed in glipizide and rosiglitazone arms than in the metformin arm. Respective figures were 4.6, 4.4,–0.5kg with intention to treat and 5.6, 6.8,–0.8kg with cohort analyses. The greatest weight gain was reported in therapy sequences C (7.2kg) D (6.4kg) and F (6.6kg) with weight reduction observed in both metformin sequences A (-1.3kg) and B (-0.3kg).

Figure 8.11: Mean weight (kg) with months from randomisation by primary therapies:

Cohort Data



Cross Sectional Data:

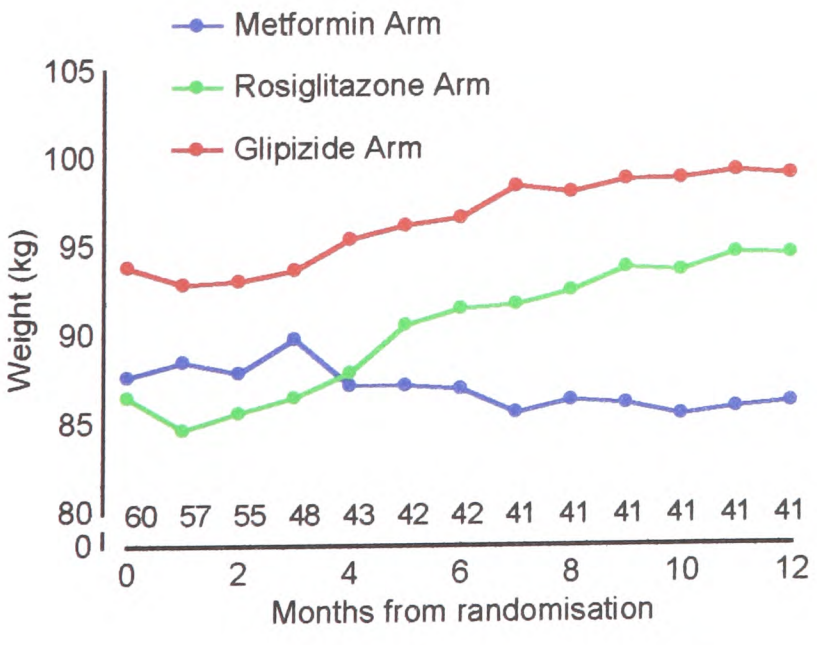


Table 8.9 : Summary Weight Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline Weight (kg)	Mean Δ Weight (kg)	Median Δ Weight (kg)
Metformin Arm	14	87.6	-0.5	-1.0
Rosiglitazone Arm	13	86.5	4.4	5.0
Glipizide Arm	14	93.8	4.6	3.0
Total	41	89.0	2.7	1.5

Anova: F = 5.57 p = 0.006 **Kruskall Wallace** : H = 12.66 p = 0.002

Cohort Analysis:

Therapy Sequence	N	Baseline Weight (kg)	Mean Δ Weight (kg)	Median Δ Weight (kg)
Metformin Arm	14	86.9	-0.8	-2.5
Rosiglitazone Arm	13	87.8	6.8	7.0
Glipizide Arm	14	93.5	5.6	3.5
Total	41	89.4	3.8	3.0

Anova : F = 6.28 p = 0.004 **Kruskall Wallace** : H = 13.45 p = 0.001

Table 8.10 : Summary Weight Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline Weight (kg)	Mean Δ Weight (kg)	Median Δ Weight (kg)
A. metformin ± humalog	11	87.6	-0.9	-1.0
B. metformin ± repaglinide	11	87.7	-0.1	-1.0
C. rosiglitazone ± humalog	8	88.4	5.3	4.5
D. rosiglitazone ± repaglinide	13	85.3	3.9	5.0
E. glipizide ± humalog	7	93.3	3.3	4.0
F. glipizide ± acarbose	10	94.2	5.5	3.0
Total	60	89.0	2.7	1.5

Anova: F = 2.36 p = 0.052 **Kruskall Wallace** : H = 13.01 p = 0.023

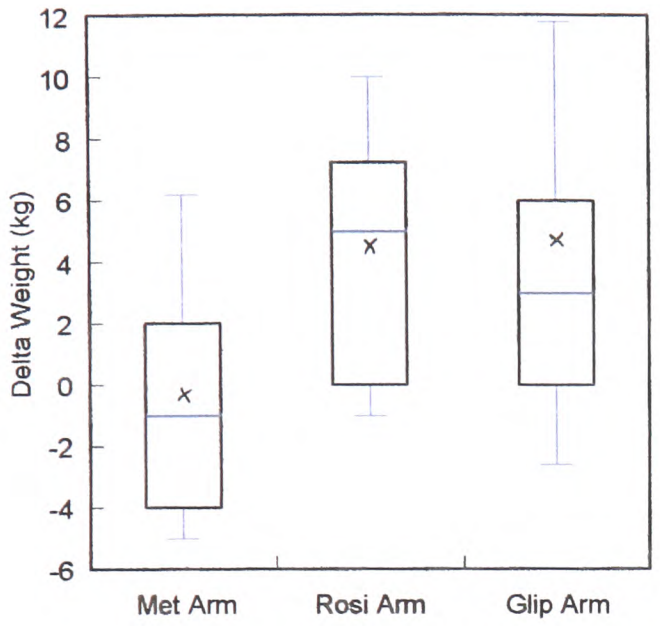
Cohort Analysis:

Therapy Sequence	N	Baseline Weight (kg)	Mean Δ Weight (kg)	Median Δ Weight (kg)
A. metformin ± humalog	7	82.7	-1.3	-3.0
B. metformin ± repaglinide	7	91.1	-0.3	-2.0
C. rosiglitazone ± humalog	6	85.7	7.2	6.0
D. rosiglitazone ± repaglinide	7	89.6	6.4	7.0
E. glipizide ± humalog	5	93.4	3.8	4.0
F. glipizide ± acarbose	9	93.6	6.6	3.0
Total	41	89.4	3.8	3.0

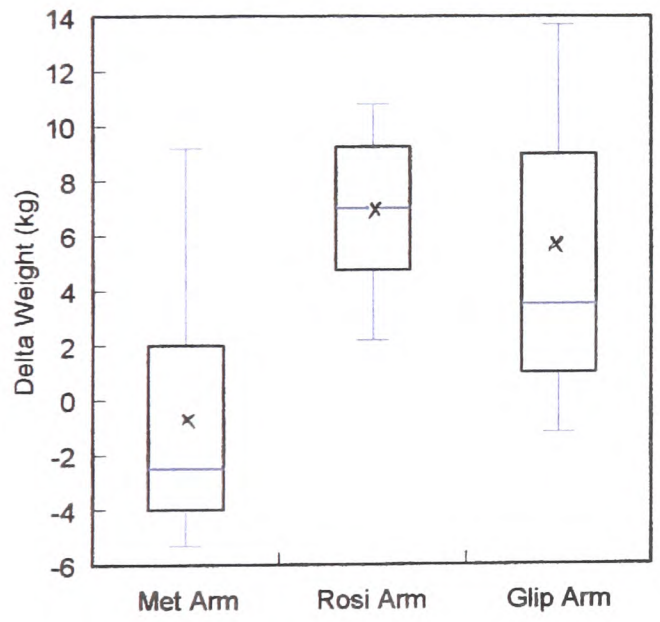
Anova : F = 2.52 p = 0.047 **Kruskall Wallace** : H = 13.6 p = 0.019

Figure 8.12: A Box Whisker Plot of ΔWeight (kg) with primary therapies

Intention to Treat Data:



Cohort Data



8.7: Blood Pressure

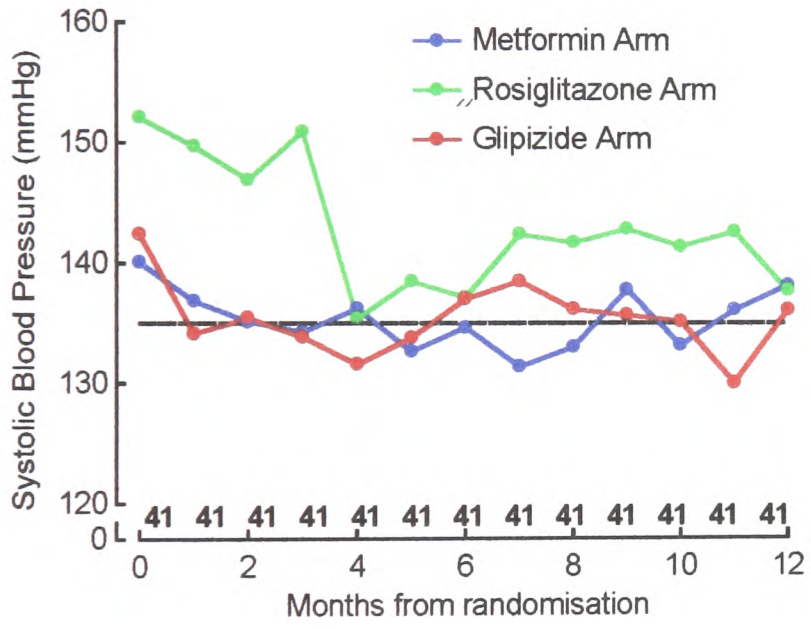
SBP increased from 141 to 142 mmHg in the metformin arm but decreased from 145 to 136 mmHg in the rosiglitazone arm and 146 to 139 mmHg in glipizide arm. No significant difference between therapy groups was seen using ANOVA analyses as shown in table 8.11 (F=2.02 p=0.143).The proportion of patients attaining SBP targets in the metformin arm decreased from 41% at baseline to 36% at one year in contrast to the improvements seen in the rosiglitazone (33% to 48%) and glipizide (18% to 41%) arms. The proportions of patients achieving SBP targets in all groups was

still relatively low at 1 year despite the repeated prompts and standardised guidelines provided for practice staff.

No significant differences in DBP between therapy algorithms was observed. Reductions from 83 to 79 mmHg in the metformin arm, 85 to 81 mmHg in rosiglitazone and 85 to 78 mmHg in glipizide arms were seen. DBP improved in all therapy arms from 46% to 59% with metformin, 29% to 62% with rosiglitazone and 47% to 59% with glipizide. The cohort analyses were similar with increases of 44% to 50%, 50% to 69% and 23% to 64% respectively for the different therapy arms. The proportions of patients achieving DBP targets was greater than those achieving SBP targets but still reached only 61% in cohort analyses.

Figure 8.13: Mean SBP (mmHg) with months from randomisation by primary therapies:

Cohort Data:



Cross Sectional Data:

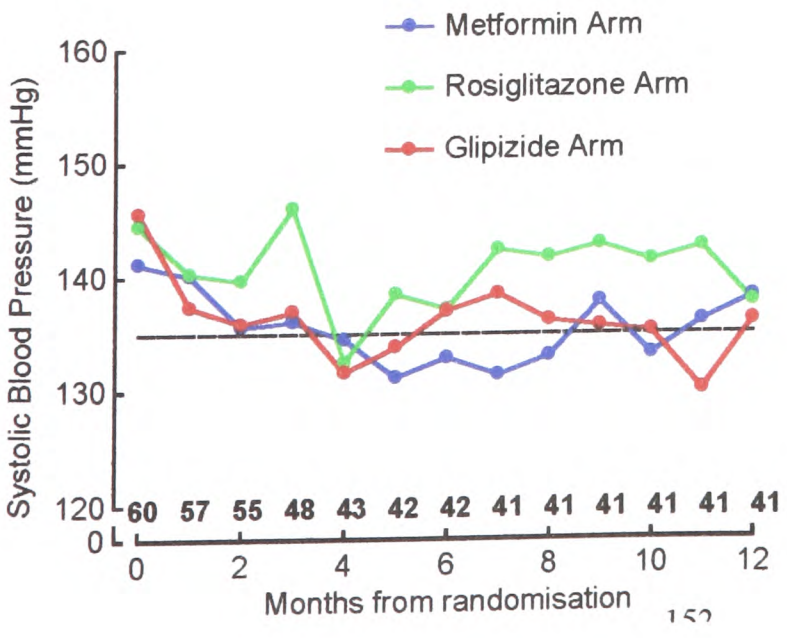


Table 8.11: Summary Systolic Blood Pressure Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline SBP (mmHg)	Mean Δ SBP (mmHg)	% SBP <135 at baseline	% SBP < 135 at one year
Metformin Arm	22	141	1	41	36
Rosiglitazone Arm	21	145	-9	33	48
Glipizide Arm	17	146	-7	18	41
Total	60	144	-5	32	42

ANOVA: F = 2.02 p = 0.143

Cohort Analysis:

Therapy Sequence	N	Baseline SBP (mmHg)	Mean Δ SBP (mmHg)	% SBP < 135 at baseline	% SBP < 135 at one year
Metformin Arm	14	133	-2	41	43
Rosiglitazone Arm	13	141	-14	33	46
Glipizide Arm	14	135	-6	18	43
Total	41	136	-7	32	44

ANOVA: F = 1.67 p = 0.202

Table 8.12: Summary Systolic Blood Pressure Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline SBP (mmHg)	Mean Δ SBP (mmHg)	% Pts with SBP < 135 at baseline	% Pts with SBP < 135 at one year
A. met ± humalog	11	136	2	55	46
B. met ± repaglinide	11	146	1	27	27
C. rosi ± humalog	8	143	-7	38	63
D. rosi ± repaglinide	13	145	-11	31	39
E. glip ± humalog	7	150	-21	14	57
F. glip ± acarbose	10	143	2	20	30
Total	60	144	-5	32	42

ANOVA: F = 2.53 p = 0.039

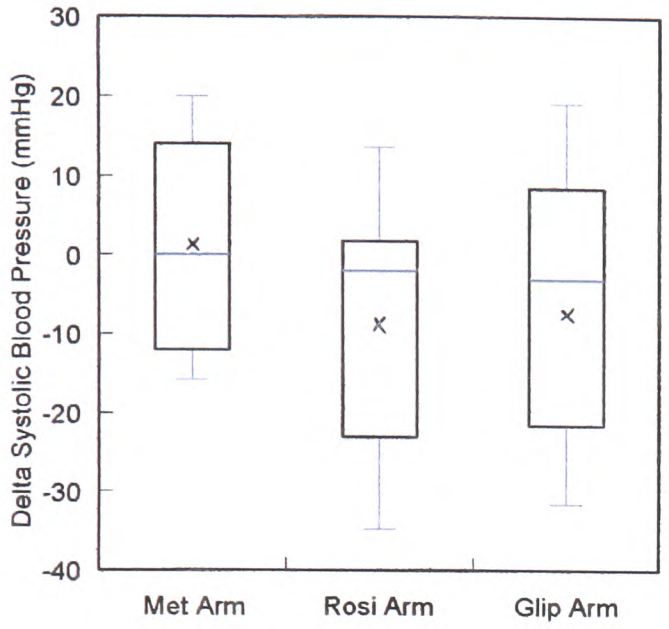
Cohort Analysis:

Therapy Sequence	N	Baseline SBP (mmHg)	Mean Δ SBP (mmHg)	% Pts with SBP < 135 at baseline	% Pts with SBP < 135 at one year
A. met ± humalog	7	135	-1	57	57
B. met ± repaglinide	7	145	-3	29	29
C. rosi ± humalog	6	150	-13	17	67
D. rosi ± repaglinide	7	154	-15	14	29
E. glip ± humalog	5	150	-23	20	60
F. glip ± acarbose	9	138	3	22	33
Total	41	145	-7	27	44

ANOVA : F = 2.33 p = 0.063

Figure 8.14 : A Box Whisker Plot of Δ SBP (mmHg) with primary therapies

Intention to Treat Data



Cohort Data

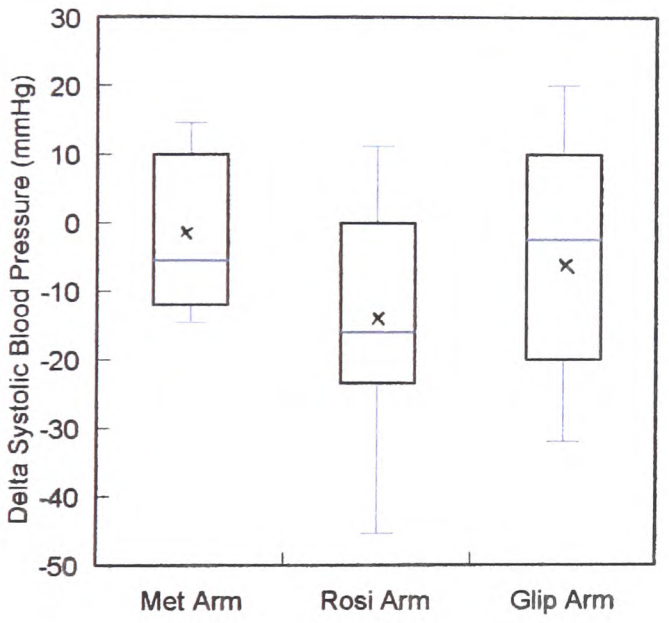
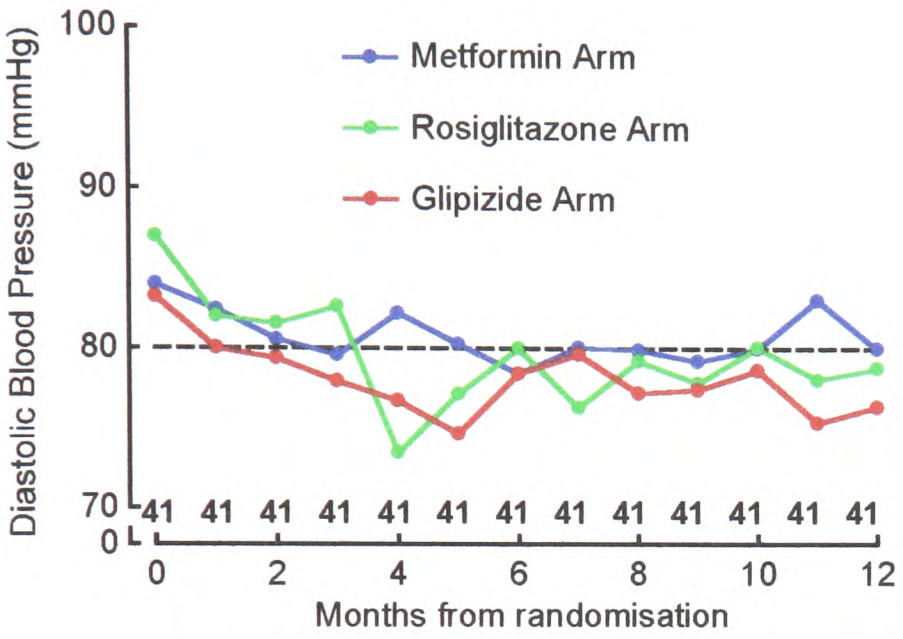


Figure 8.15 : Mean DBP (mmHg) with months from randomisation for primary therapies

Cohort Data



Cross Sectional Data

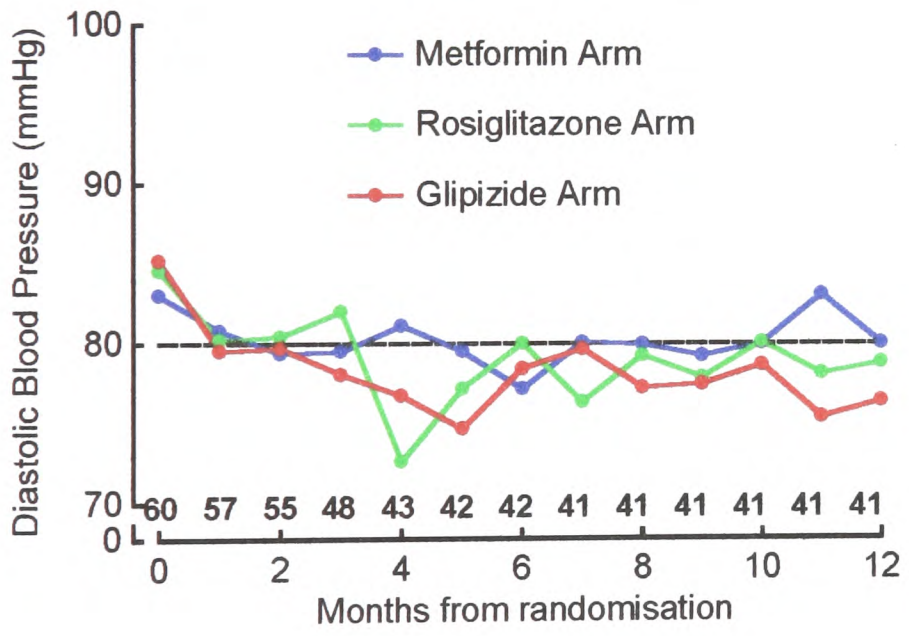


Table 8.13: Summary DBP Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline DBP (mmHg)	Mean Δ DBP (mmHg)	% Pts < 80 at baseline	% Pts < 80 at one year
Metformin Arm	22	83	-4	46	59
Rosiglitazone Arm	21	85	-4	29	62
Glipizide Arm	17	85	-7	47	59
Total	60	84	-5	40	60

ANOVA: F = 0.62 p = 0.54

Cohort Analysis:

Therapy Sequence	N	Baseline DBP (mmHg)	Mean Δ DBP (mmHg)	% Pts < 80 at baseline	% Pts < 80 at one year
Metformin Arm	14	84	-4	44	50
Rosiglitazone Arm	13	87	-8	50	69
Glipizide Arm	14	83	-7	23	64
Total	41	85	-6	57	61

ANOVA: F = 0.46 p = 0.635

Table 8.14: Summary DBP Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline DBP (mmHg)	Mean Δ DBP (mmHg)	% Pts with DBP < 80 at baseline	% Pts with DBP < 80 at one year
A. metformin ± humalog	11	80	-4	55	73
B. metformin ± repaglinide	11	86	-4	36	46
C. rosiglitazone ± humalog	8	85	-4	25	63
D. rosiglitazone ± repaglinide	13	84	-4	31	62
E. glipizide ± humalog	7	89	-17	29	86
F. glipizide ± acarbose	10	83	-1	60	40
Total	60	84	-5	40	60

ANOVA: F = 2.06 p = 0.085

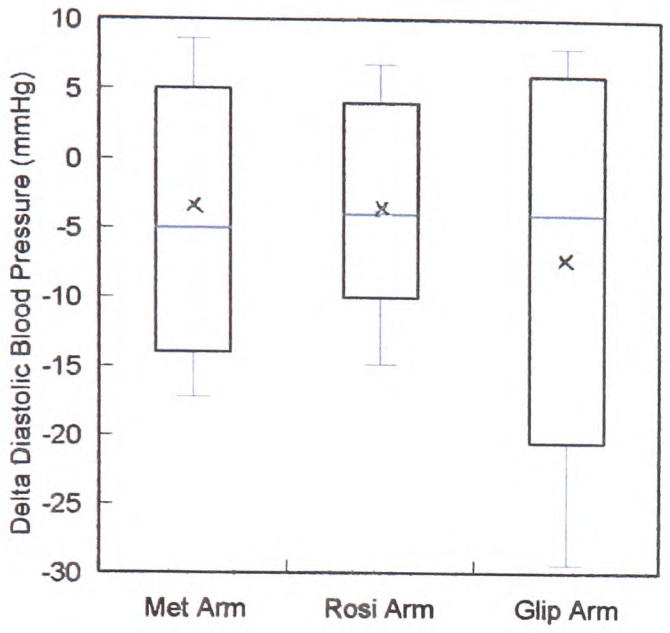
Cohort Analysis:

Therapy Sequence	N	Baseline DBP (mmHg)	Mean Δ DBP (mmHg)	% Pts with DBP < 80 at baseline	% Pts with DBP < 80 at one year
A. metformin ± humalog	7	80	-2	43	57
B. metformin ± repaglinide	7	88	-6	29	43
C. rosiglitazone ± humalog	6	86	-6	17	67
D. rosiglitazone ± repaglinide	7	88	-10	29	71
E. glipizide ± humalog	5	87	-19	40	100
F. glipizide ± acarbose	9	81	0	67	44
Total	41	85	-6	44	61

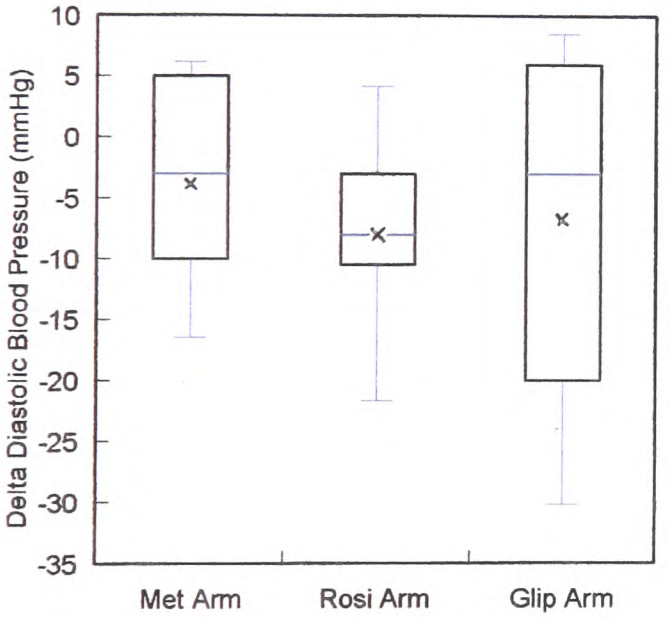
ANOVA: F = 2.49 p = 0.05

Figure 8.16: A Box Whisker Plot of Δ DBP with primary therapies

Intention to Treat Data



Cohort Data



8.8 Lipid Changes

A modest improvement in total cholesterol (p=0.189) was seen overall with 48% patients achieving targets at baseline compared to 63% at one year. This trend was seen in all therapy groups with an increase from 45% to 63% in the metformin arm, 57% to 67% in the rosiglitazone arm and 41% to 65% with glipizide. No significant differences between therapy groups were seen although there was a trend to a lesser improvement in proportion achieving total cholesterol targets in therapy group C. Mean total cholesterol was reduced by –0.3mmol/L in the glipizide arm compared to –0.2 with metformin and –0.1 with rosiglitazone arms.

The results for each treatment arm are shown in the tables below. Baseline LDL was greatest in the metformin arm and a non-significant trend toward a greater reduction with rosiglitazone therapy was observed. A greater proportion of patients achieved target values with therapy sequence A in the ITT and A, D and E in the cohort analyses but again no significant differences between therapy sequences were observed.

The mean overall increase in HDL during the study was 0.06 mmol/L with greater changes in the metformin (0.09) compared to the rosiglitazone (0.05) and glipizide (0.03) arms. A trend towards a greater proportion of patients achieving HDL-cholesterol targets in the metformin and glipizide groups was seen although no significant differences between therapy sequences were apparent. The proportion of patients attaining HDL-cholesterol targets in the rosiglitazone groups remained unchanged in protocol-adherent patients (85%) and infact declined with ITT analyses (81% to 76%). The variability of HDL results was greatest in the metformin therapy arm.

Baseline TG was greatest in the glipizide arm at 3.07 mmol/L with a greater mean delta observed (–0.88mmol/L) compared to the metformin (–0.12mmol/L) and rosiglitazone (–0.04mmol/L) arms. No significant differences between therapy sequences were seen.

Table 8.15: Summary Total Cholesterol (TC) Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline TC (mmol/l)	Mean ΔTC (mmol/l)	% Pts with TC < 5.2 at baseline	% Pts with TC < 5.2 at one year
Metformin Arm	22	5.2	-0.2	45	59
Rosiglitazone Arm	21	4.9	-0.1	57	67
Glipizide Arm	17	5.3	-0.3	41	65
Total	60	5.1	-0.3	48	63

ANOVA: F = 0.21 p = 0.815

Cohort Analysis:

Therapy Sequence	N	BaselineTC (mmol/l)	Mean ΔTC (mmol/l)	% Pts with TC < 5.2 at baseline	% Pts with TC < 5.2 at one year
Metformin Arm	14	5.1	0.1	50	64
Rosiglitazone Arm	13	4.9	0.1	54	62
Glipizide Arm	14	5.2	-0.3	43	64
Total	41	5.1	-0.1	49	63

ANOVA: F = 0.79 p = 0.46

Table 8.16: Summary Total Cholesterol Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline TC (mmol/l)	Mean Δ TC (mmol/l)	% Pts with TC < 5.2 at baseline	% Pts with TC < 5.2 at one year
A. met ± humalog	11	5.1	0.1	45	55
B. met ± repaglinide	11	5.3	-0.3	45	64
C. rosi ± humalog	8	4.7	0.2	75	63
D. rosi ± repaglinide	13	5.1	-0.5	46	69
E. glip ± humalog	7	5.6	-0.6	43	71
F. glip ± acarbose	10	5.1	-0.02	40	60
Total	60	5.1	-0.2	48	63

ANOVA: F = 0.84 p = 0.525

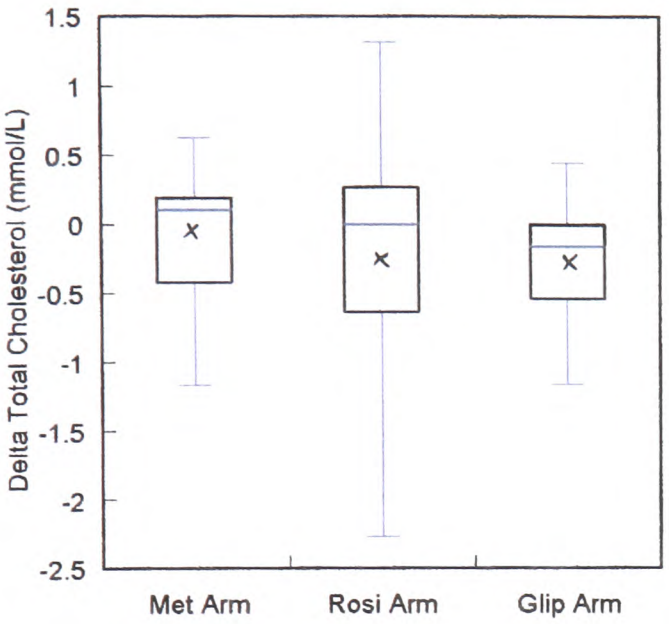
Cohort Analysis:

Therapy Sequence	N	Baseline TC (mmol/l)	Mean Δ TC (mmol/l)	% Pts with TC < 5.2 at baseline	% Pts with TC < 5.2 at one year
A. met ± humalog	7	5.0	-0.1	43	57
B. met ± repaglinide	7	5.1	0.2	57	71
C. rosi ± humalog	6	4.8	-0.1	67	67
D. rosi ± repaglinide	7	5.1	0.1	43	57
E. glip ± humalog	5	5.5	-0.9	40	80
F. glip ± acarbose	9	5.1	0.0	44	56
Total	41	5.1	-0.1	49	63

ANOVA: F = 1.04 p = 0.41

Figure 8.17: A Box Whisker Plot of Delta Total Cholesterol (mmol/L) with primary therapies

Intention to Treat Data



Cohort Data

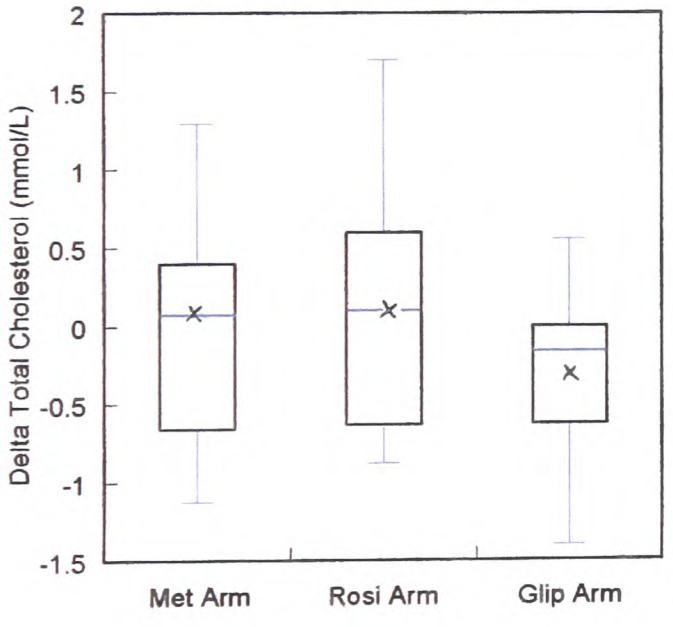


Table 8.17: Summary LDL-Cholesterol Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline LDL (mmol/l)	Mean Δ LDL-Chol (mmol/l)	% LDL<3.4 at baseline	% LDL < 3.4 at one year
Metformin Arm	22	3.28	0.03	50	59
Rosiglitazone Arm	21	3.11	-0.01	57	62
Glipizide Arm	17	3.09	0.07	65	71
Total	60	3.17	0.03	57	63

ANOVA: F = 0.08 p = 0.925

Cohort Analysis:

Therapy Sequence	N	Baseline LDL (mmol/l)	Mean Δ LDL-Chol (mmol/l)	% LDL<3.4 at baseline	% LDL < 3.4 at one year
Metformin Arm	14	3.18	0.01	50	71
Rosiglitazone Arm	13	3.12	-0.01	54	62
Glipizide Arm	14	3.12	0.03	57	64
Total	41	3.14	0.01	54	66

ANOVA: F = 0.01 p = 0.988

Table 8.18: Summary LDL-Cholesterol Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline LDL (mmol/l)	Mean ΔLDL (mmol/l)	% Pts with LDL < 3.4 at baseline	% Pts with LDL < 3.4 at one year
A. met ± humalog	11	3.28	-0.02	55	73
B. met ± repaglinide	11	3.29	0.08	45	45
C. rosi ± humalog	8	3.15	0.04	63	63
D. rosi ± repaglinide	13	3.09	-0.04	54	54
E. glip ± humalog	7	2.88	0.12	71	71
F. glip ± acarbose	10	3.23	0.03	60	60
Total	60	3.17	0.03	57	63

ANOVA: F = 0.10 p = 0.992

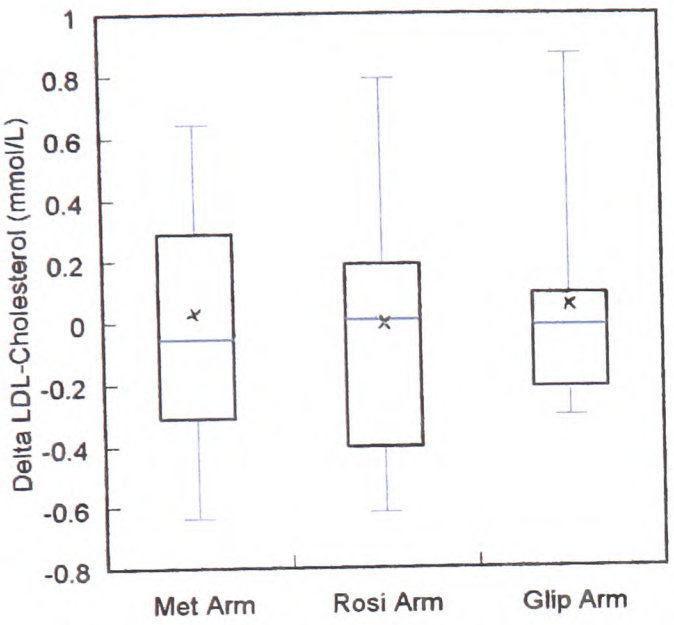
Cohort Analysis:

Therapy Sequence	N	Baseline LDL (mmol/l)	Mean ΔLDL (mmol/l)	% Pts with LDL < 3.4 at baseline	% Pts with LDL < 3.4 at one year
A. met ± humalog	7	3.27	-0.01	43	86
B. met ± repaglinide	7	3.10	0.04	57	57
C. rosi ± humalog	6	3.11	-0.01	50	50
D. rosi ± repaglinide	7	3.13	-0.01	57	71
E. glip ± humalog	5	2.90	-0.03	60	80
F. glip ± acarbose	9	3.24	0.06	56	56
Total	41	3.14	0.01	54	66

ANOVA: F = 0.02 p = 1.000

Figure 8.18: A Box Whisker Plot of Delta LDL-Cholesterol with primary therapies

Intention to Treat Data



Cohort Data

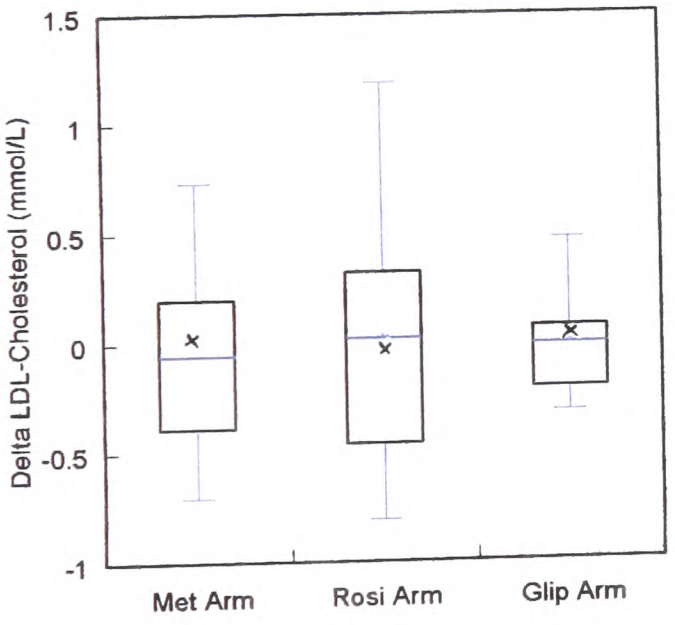


Table 8.19: Summary HDL-Cholesterol Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline HDL (mmol/l)	Mean Δ HDL-Chol (mmol/l)	% HDL <1.1 at baseline	% HDL <1.1 at one year
Metformin Arm	22	1.25	0.09	59	64
Rosiglitazone Arm	21	1.28	0.05	81	76
Glipizide Arm	17	1.10	0.03	53	65
Total	60	1.22	0.06	65	68

ANOVA: F = 0.35 p = 0.708

Cohort Analysis:

Therapy Sequence	N	Baseline HDL (mmol/l)	Mean Δ HDL-Chol (mmol/l)	% HDL <1.1 at baseline	% HDL <1.1 at one year
Metformin Arm	14	1.15	0.17	57	64
Rosiglitazone Arm	13	1.23	0.09	85	85
Glipizide Arm	14	1.11	0.01	50	64
Total	41	1.16	0.09	63	71

ANOVA: F = 1.97 p = 0.154

Table 8.20: Summary HDL-Cholesterol Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline HDL-Chol (mmol/l)	Mean Δ HDL-Chol (mmol/l)	% Pts with HDL > 1.1 at baseline	% Pts with HDL >1.1 at one year
A. met ± humalog	11	1.17	0.22	64	64
B. met ± repaglinide	11	1.33	-0.04	55	64
C. rosi ± humalog	8	1.15	0.10	63	63
D. rosi ± repaglinide	13	1.37	0.03	92	85
E. glip ± humalog	7	1.06	-0.01	43	57
F. glip ± acarbose	10	1.13	0.05	60	70
Total	60	1.22	0.06	25	40

ANOVA: F = 1.62 p = 0.170

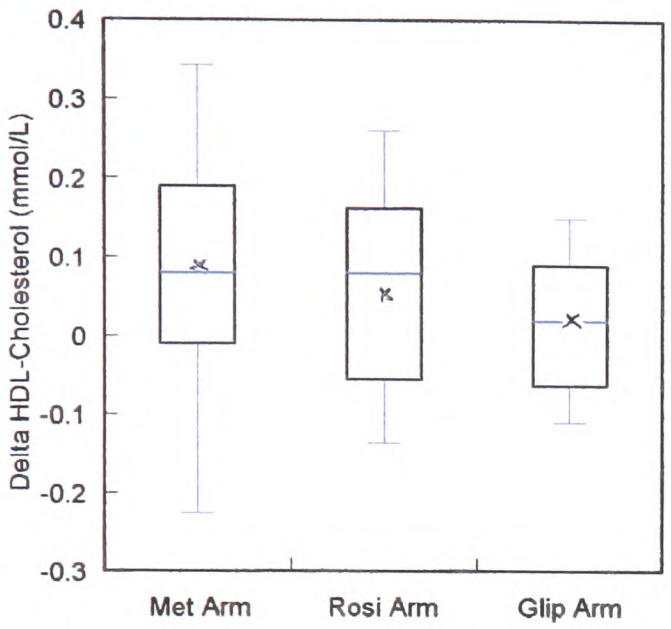
Cohort Analysis:

Therapy Sequence	N	Baseline HDL-Chol (mmol/l)	Mean Δ HDL-Chol (mmol/l)	% Pts with HDL > 1.1 at baseline	% Pts with HDL >1.1 at one year
A. met ± humalog	7	1.19	0.27	71	71
B. met ± repaglinide	7	1.11	0.07	43	57
C. rosi ± humalog	6	1.19	0.09	83	67
D. rosi ± repaglinide	7	1.26	0.09	86	100
E. glip ± humalog	5	1.09	0.00	40	60
F. glip ± acarbose	9	1.12	0.02	56	67
Total	41	1.16	0.09	63	71

ANOVA: F = 1.45 p = 0.230

Figure 8.19: A Box Whisker Plot of Delta HDL-Cholesterol (mmol/L) with primary therapies

Intention to Treat Data



Cohort Data

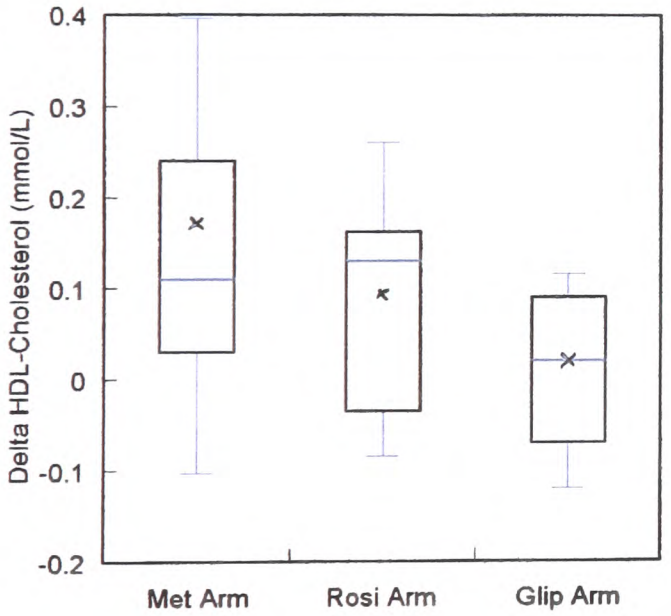


Table 8.21: Summary VLDL-Cholesterol Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline VLDL (mmol/l)	Mean Δ VLDL (mmol/l)
Metformin Arm	22	0.66	-0.03
Rosiglitazone Arm	21	0.53	0.02
Glipizide Arm	17	1.15	-0.36
Total	60	0.75	-0.10

ANOVA: F = 3.41 p = 0.040

Cohort Analysis:

Therapy Sequence	N	Baseline VLDL (mmol/l)	Mean ΔVLDL (mmol/l)
Metformin Arm	14	0.73	-0.09
Rosiglitazone Arm	13	0.57	0.02
Glipizide Arm	14	1.00	-0.36
Total	41	0.77	-0.15

ANOVA: F = 1.62 p = 0.212

Table 8.22: Summary VLDL-Cholesterol Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline VLDL-Chol (mmol/l)	Mean Δ VLDL-Chol (mmol/l)
A. metformin ± humalog	11	0.59	-0.05
B. metformin ± repaglinide	11	0.72	0.00
C. rosiglitazone ± humalog	8	0.41	0.03
D. rosiglitazone ± repaglinide	13	0.61	0.02
E. glipizide ± humalog	7	1.69	-0.74
F. glipizide ± acarbose	10	0.77	-0.10
Total	60	0.75	-0.10

ANOVA: F = 3.08 p = 0.016

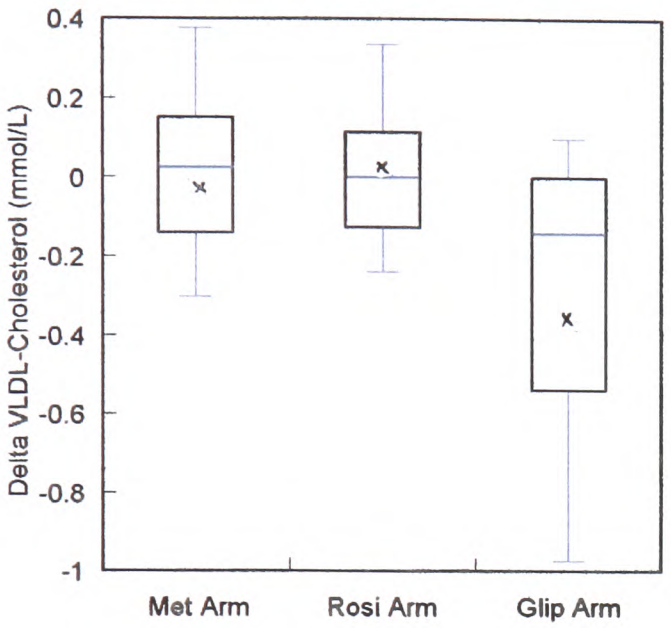
Cohort Analysis:

Therapy Sequence	N	Baseline VLDL-Chol (mmol/l)	Mean Δ VLDL-Chol (mmol/l)
A. metformin ± humalog	7	0.57	0.00
B. metformin ± repaglinide	7	0.89	-0.18
C. rosiglitazone ± humalog	6	0.45	0.03
D. rosiglitazone ± repaglinide	7	0.68	0.01
E. glipizide ± humalog	5	1.52	-0.90
F. glipizide ± acarbose	9	0.71	-0.05
Total	41	0.77	-0.15

ANOVA: F = 2.56 p = 0.045

Figure 8.20: A Box Whisker Plot of Delta VLDL-Cholesterol with primary therapies

Intention to Treat Data



Cohort Data

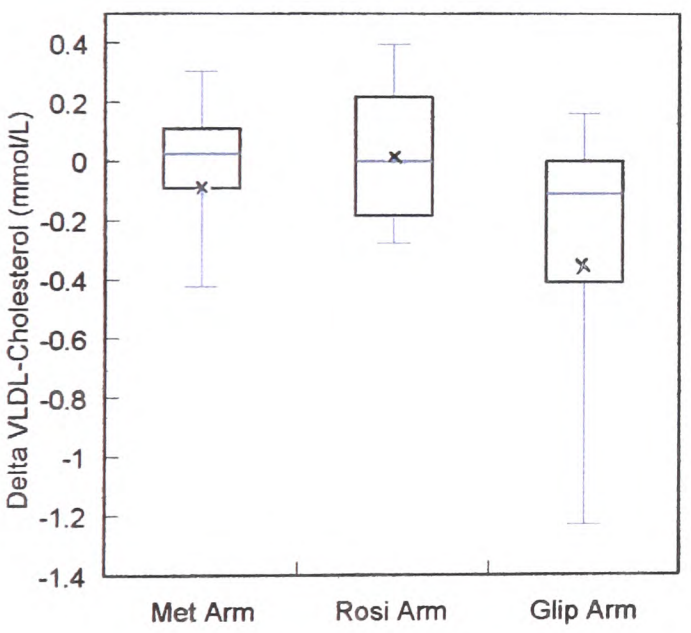


Table 8.23: Summary Triglyceride Results: Primary Therapies

Intention to Treat Analysis:

Therapy Sequence	N	Baseline TG (mmol/l)	Mean Δ TG (mmol/l)	% Pts with TG < 1.7 mmol/l
Metformin Arm	22	1.74	-0.12	68
Rosiglitazone Arm	21	1.45	-0.04	67
Glipizide Arm	17	3.07	-0.88	35
Total	60	2.01	-0.31	58

ANOVA: F = 1.76 p = 0.182

Cohort Analysis:

Therapy Sequence	N	Baseline TG (mmol/l)	Mean Δ TG (mmol/l)	% Pts with TG < 1.7 mmol/l
Metformin Arm	14	1.97	-0.34	71
Rosiglitazone Arm	13	1.52	-0.22	85
Glipizide Arm	14	2.77	-1.00	36
Total	41	2.10	-0.53	63

ANOVA: F = 0.84 p = 0.439

Table 8.24: Summary Triglyceride Results: Individual Therapy Sequences

Intention to Treat Analysis:

Therapy Sequence	N	Baseline TG (mmol/l)	Mean Δ TG (mmol/l)	% Pts with TG < 1.7 at baseline	% Pts with TG < 1.7 at one year
A. metformin ± humalog	11	1.52	-0.06	55	82
B. metformin ± repaglinide	11	1.96	-0.19	82	55
C. rosiglitazone ± humalog	8	1.20	-0.04	88	75
D. rosiglitazone ± repaglinide	13	1.61	-0.03	77	62
E. glipizide ± humalog	7	4.72	-1.81	29	29
F. glipizide ± acarbose	10	1.91	-0.22	30	40
Total	60	2.01	-0.31	62	58

ANOVA: F = 1.03 p = 0.411

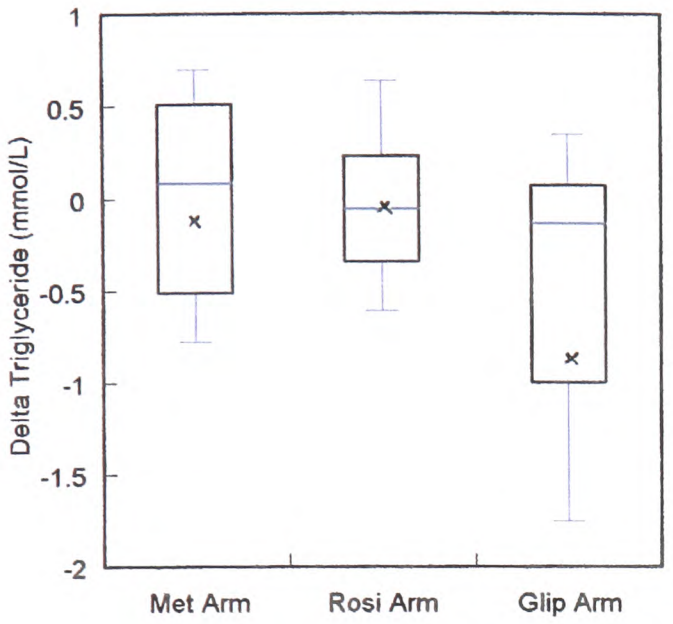
Cohort Analysis:

Therapy Sequence	N	Baseline TG (mmol/l)	Mean Δ TG (mmol/l)	% Pts with TG < 1.7 at baseline	% Pts with TG < 1.7 at one year
A. metformin ± humalog	7	1.43	0.00	57	86
B. metformin ± repaglinide	7	2.51	-0.69	71	57
C. rosiglitazone ± humalog	6	1.35	-0.24	83	83
D. rosiglitazone ± repaglinide	7	1.67	-0.20	86	86
E. glipizide ± humalog	5	4.51	-2.51	20	20
F. glipizide ± acarbose	9	1.81	-0.16	33	44
Total	41	2.10	-0.53	59	63

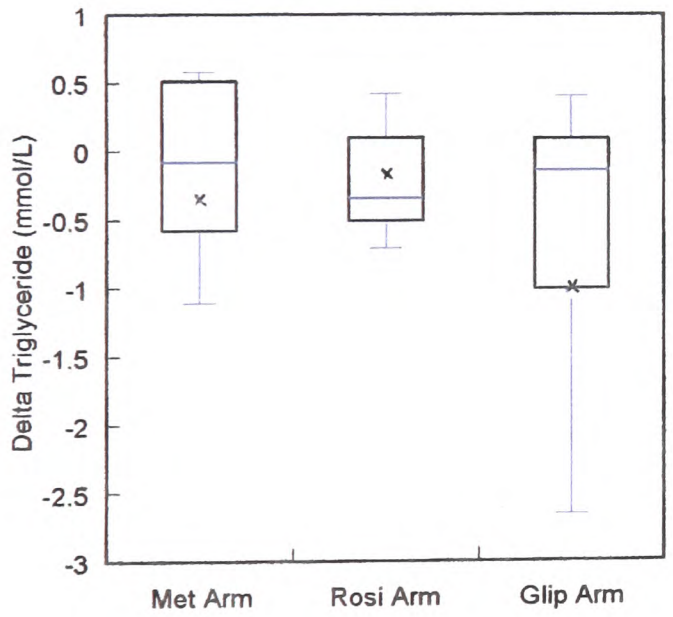
ANOVA: F = 1.14 p = 0.360

Figure 8.21: A Box Whisker Plot of Delta TG (mmol/L) with primary therapies

Intention to Treat Data



Cohort Data



8.9: Cardiac risk

8.9.1: Calculated CHD risk

Table 8.25: Summary CHD Risk Results

Intention to Treat Analysis:

Therapy Sequence	N	Mean (SD) Risk Baseline (%)	Mean (SD) Risk One Year (%)	Mean Δ Risk (%)
Metformin Arm	22	19.0 (8.8)	16.2 (7.8)	-2.8
Rosiglitazone Arm	21	18.1 (6.6)	16.7 (6.2)	-1.4
Glipizide Arm	17	21.0 (9.0)	17.7 (9.7)	-3.3
Total	60	19.3 (8.1)	16.8 (7.8)	-2.5

ANOVA: F=0.37 p=0.691

Cohort Analysis:

Therapy Sequence	N	Mean (SD) Risk Baseline (%)	Mean (SD) Risk Closeout (%)	Mean Δ Risk (%)
Metformin Arm	14	20.0 (9.7)	17.2 (8.0)	-2.8
Rosiglitazone Arm	13	20.3 (5.7)	17.8 (7.5)	-2.5
Glipizide Arm	14	20.0 (9.8)	17.9 (10.9)	-2.1
Total	41	20.1 (8.5)	17.6 (8.7)	-2.5

ANOVA: F=0.03 p=0.974

8.9.2: Calculated CVA Risk

Table 8.26: Summary CVA Risk Results

Intention to Treat Analysis:

Therapy Sequence	N	Mean (SD) Risk Baseline (%)	Mean (SD) Risk Closeout (%)	Mean Δ Risk (%)
Metformin Arm	22	6.7 (5.6)	7.6 (4.8)	0.9
Rosiglitazone Arm	21	8.2 (5.3)	6.3 (3.3)	-1.9
Glipizide Arm	17	6.2 (4.6)	6.2 (4.9)	0.0
Total	60	7.2 (4.5)	6.8 (4.3)	-0.4

ANOVA: F=1.76 p=0.182

Cohort Analysis:

Therapy Sequence	N	Mean (SD) Risk Baseline (%)	Mean (SD) Risk Closeout (%)	Mean Δ Risk (%)
Metformin Arm	14	8.0 (6.0)	7.9 (5.2)	-0.1
Rosiglitazone Arm	13	9.1 (3.7)	7.0 (3.7)	-2.1
Glipizide Arm	14	5.4 (3.5)	5.3 (3.2)	-0.1
Total	41	7.5 (4.7)	6.7 (4.2)	-0.8

ANOVA: F=1.28 p=0.290

No significant differences in baseline CVD risk factors were present between therapy groups. Calculated CVD risk and markers were also similar between therapy groups at baseline and one year with only Lp(a) differing significantly between arms. Metformin patients had significantly greater Lp(a) than those in glipizide or rosiglitazone arms at both timepoints.

No significant differences in CVD risk factor reduction was observed in different therapy groups with the exception of tPA which increased in the metformin arm, remained stable with glipizide and decreased in the rosiglitazone arm (Lpa p=0.152, tPA p=0.014, Homocysteine p=0.341, dDimer p=0.844).

Table 8.27: Cardiovascular Risk Data : Baseline Results

	Met Arm N=22	**Rosi Arm** N=21	**Glip Arm** N=17	**P**
Demographic				
Gender (M/F)	15/7	13/8	10/7	0.80
Age (years)*	60.7 (9.0)	63.3 (7.6)	58.3 (7.5)	0.17
Clinical				
Weight (kg)*	87.6 (15.5)	86.5 (13.7)	93.8 (14.9)	0.28
BMI (kg/m^2)*	30.0 (3.8)	29.9 (5.2)	32.2 (5.7)	0.29
SBP (mmHg)*	141.1 (16.7)	144.5 (19.6)	145.6 (15.3)	0.70
DBP (mmHg)*	83.0 (10.0)	84.6 (12.5)	85.2 (10.4)	0.81
Smoking No/ex/cur (%)	36/55/9	19/62/19	35/41/24	0.50
CVS Risk Markers				
Total chol (mmol/L)*	5.2 (0.7)	4.9 (0.5)	5.3 (1.3)	0.45
HDL-chol (mmol/L)*	1.3 (0.5)	1.3 (0.3)	1.1 (0.2)	0.30
Lpa	385.8 (444.1)	112.8 (102.8)	89.1 (145.3)	0.002
TPA	10.8 (3.5)	12.5 (7.0)	11.1 (3.4)	0.49
HsCRP	5.4 (5.9)	10.5 (16.5)	6.1 (4.6)	0.26
D-dimer	114.2 (198.9)	124.8 (138.4)	88.2 (62.9)	0.75
Homocysteine	15.0 (3.9)	17.5 (8.1)	17.1 (4.8)	0.36
Complications				
IHD (%)	4 (18)	3 (14)	1 (6)	---
PVD (%)	0	0	1 (6)	---
CVD (%)	0	0	0	---
Calculated CHD Risk				
Mean CHD Risk – SBP	19.0 (8.8)	18.1 (6.6)	21.0 (9.0)	0.56
Mean CHD Risk – DBP	18.5 (8.9)	18.5 (6.9)	20.5 (8.5)	0.70
Mean CVA Risk – SBP	7.0 (5.3)	7.6 (3.7)	6.9 (4.7)	0.88
Mean CVA Risk – DBP	6.7 (5.6)	8.2 (5.3)	6.2 (4.6)	0.45

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

Table 8.28: Cardiovascular Risk Data : One Year Results

	Met Arm N=22	**Rosi Arm** N=21	**Glip Arm** N=17	**P**
Demographic				
Gender (M/F)	15/7	13/8	10/7	0.80
Age (years)*	61.7 (9.0)	64.3 (7.6)	59.3 (7.5)	0.17
Clinical				
Weight (kg)*	87.2 (16.8)	90.9 (15.2)	98.4 (20.2)	0.14
BMI (kg/m^2)*	29.8 (4.3)	31.4 (5.7)	33.6 (6.9)	0.15
SBP (mmHg)*	138.1 (18.9)	137.7 (11.1)	136.1 (17.8)	0.43
DBP (mmHg)*	80.0 (10.4)	78.8 (7.8)	76.3 (11.3)	0.61
Smoking No/ex/cur (%)	36/55/9	19/62/19	35/41/24	0.50
CVS Risk Markers				
Total chol (mmol/L)*	5.1 (0.2)	4.7 (2.2)	5.1 (1.0)	0.38
HDL-chol (mmol/L)*	1.3 (0.3)	1.3 (0.3)	1.1 (0.2)	0.08
Lpa	400.8 (444.6)	162.9 (138.3)	110.6 (154.9)	0.006
tPA	12.1 (5.6)	9.3 (3.7)	11.1 (3.6)	0.13
hsCRP	6.4 (12.7)	5.3 (7.4)	6.8 (5.9)	0.87
D-dimer	88.1 (82.7)	120.3 (110.3)	86.4 (66.6)	0.40
Homocysteine	15.3 (4.2)	17.8 (8.2)	16 (5.9)	0.41
Complications				
IHD (%)	4 (18)	3 (14)	1 (6)	---
PVD (%)	0	0	1 (6)	---
CVD (%)	0	0	0	---
Calculated CVS Risk				
Mean CHD Risk – SBP	16.2	16.7	17.7	0.83
Mean CHD Risk – DBP	14.7	17.2	16.8	0.55
Mean CVA Risk – SBP	7.6	6.3	6.2	0.52
Mean CVA Risk – DBP	6.3	7.0	5.4	0.54

*Data are % of group, *mean (SD), †median (IQR), or ‡ geometric mean (1SD range)*

Section Four: Discussion and Conclusions

Chapter 9 : Discussion

9.1. Study Strengths

This work provides a synthesis of the literature relating to glucose optimisation in T2DM highlighting issues of central importance to primary care. It provides a foundation for translation of evidence-based research findings for optimal T2DM care into routine clinical practice and develops methodology to enable OHA intensification, insulin initiation and titration to be accomplished safely and effectively in general practices. It assesses the feasibility of a RCT of biguanide versus TZD agents on cardiovascular events in primary care and provides important information for the design and conduct of large-scale clinical outcome trials.

The approach used within this study is original and extends current knowledge in the field. Unlike most other studies of glucose optimisation it is undertaken in primary care and enables particular difficulties in this situation to be explored. It makes use of existing practice nurses and examines the training and support required for protocol-driven glucose optimisation and insulin initiation to be accomplished in primary care. The treat to target approach has only really been emphasised since the publication of the UKPDS results in 1998 and the tighter glucose targets emphasised in the study go beyond those used in UKPDS, DCCT and the ADA reflecting already the most recent recommendations from NICE, WHO and AACE. The emphasis placed on fasting and prandial glucose monitoring and control has not been previously trialed in general practice and selection of OHA combinations for this purpose is also new. Novel titration schedules, treatment algorithms individualised treatment plans for patients outlining the therapy progression if glucose targets are exceeded and monitoring guidelines also add to the originality of this approach. This study provides the structure for large-scale trials to compare CVS risk benefits with metformin and TZD agents and will thus help clarify the optimal first-line agent for use in T2DM. It also provides an integral educational programme to run concurrently with glucose optimisation and CVS risk management in primary care and teaching plans to assist nurses to relay practical skills to patients.

This work had a broad remit focusing not only on just the feasibility of attaining normoglycaemia and CVS risk factor modification in primary care but also on the acceptability, adherence, safety and QoL issues to patients. An observational comparison with standard practice care, exploration of potential benefits of glucose optimisation and discussion of potential barriers to its generalisability are discussed.

The methodological design of the study was tailored to the broad objectives and outcomes expected. It was designed with a feasibility context in mind to inform the design of further definitive research. The study used existing therapies, staff and services enhancing the generalisability of conclusions to other practice settings. It was also a randomised clinical trial design and despite its small size used comprehensive central randomisation procedures and minimisation criteria to ensure the balanced allocation of patients to therapy groups. Its structure enabled direct comparison of glucose and CVS outcomes with the three primary therapy arms and permitted the benefits of biguanides versus TZD and sulphonylurea agents to be elicited. Allocation of patients to similar second line agents avoiding drug crossover and substitution problems inherent in other studies maintained this pure comparison of primary therapies. The small size and feasibility structure was advantageous to explore clinical, biochemical and patient outcomes before extrapolation to major clinical trials but does not have the power to produce definitive conclusions. The observational versus randomised comparison of novel versus standard practice care also does not permit a clear statement of superiority of the former.

Effective strategies for OHA titration are poorly documented in the literature and novel schedules were used in this study. Schedules were designed to be safe, effective and simple for primary care use. The Holman-Turner method has been used extensively in hospital settings and was adapted for primary care use with few problems. The gating technique for glucose optimisation based on the last fortnight of glucose values captured the effects of therapy increases once values had stabilised. This approach was highly acceptable to nurses and patients. The gating threshold was selected from experience in hospital diabetes and practice clinics. Safety criteria were included such that therapy was not increased where target glucose or HbA_{1c} values were met or where a proven hypoglycaemia episode had occurred within the last month. This technique is similar to that described by Matthew Riddle. Flexibility in the gating approach was included for concurrent illness, shift work, foreign travel and religious festivals. Where a differential between FPG and HbA_{1c} data existed HBGM techniques were checked, meters recalibrated and haemoglobinopathy screening undertaken. A sliding scale was developed with titration doses based on a 4-unit increase in insulin units for every 1mmol/l above FPG or PPG target values adjusted for BMI. All practice nurses were comfortable with the adjustment of OHA and insulin doses using the algorithms by the end of the study.

Recruitment was maximised by searching computer and manual diabetic registers and records for eligible patients, sending a detailed invitation letter to all those identified and individually contacting all potential participants by telephone to discuss study details and queries. Comprehensive data on the characteristics of recruited and non-recruited groups and principal reason for non-participation was collected to enable extrapolation of the programme to a wider population of T2DM patients.

A detailed programme of education was developed to run concurrently with the glucose optimisation and cardiovascular risk modification strategy to enhance patient knowledge and outcomes. Provision of individualised therapy plans for patients emphasising predicted therapy increases if glucose targets were exceeded was useful highlighting the progressive nature of type 2 diabetes and the intensification of therapy required to combat declining beta-cell function. Most patients commented that they had been unaware of the progressive nature of the disease and felt that dietary control and lifestyle change would be sufficient to ward off insulin use. Although four patients reported a slight increase in anxiety with the plans they were generally well-liked and increased both understanding and acceptability of glucose optimisation. Equally all patients became aware of fasting and prandial targets for home monitoring in the study and contrasted this with their lack of prior knowledge of these values. At the end of the study most patients were aware of the meaning and value of their HbA_{1c} measures for the first time in their illness. The diet, exercise, smoking cessation leaflets and insulin initiation programme designed for the study were well received by nurses and patients and although knowledge and self-management skills were not tested formally marked subjective improvement occurred. The combination of teaching plans with nurse fact-files and patient leaflets worked well and all nurses reporting increased knowledge and confidence with T2DM and insulin management at the end of the study.

Data accuracy and completeness was enhanced with clinic task prompts, SOPs, data checking and biochemical laboratory quality assurance tests. Data was displayed using not only ITT analyses but also cohort statistics to evaluate any potential differences between the entire group and withdrawing patients. Use of appropriate statistical tests was cross-checked by a qualified statistician.

9.2. Potential limitations

The broad remit, numerous objectives and feasibility context of this project made the definition of a single study design complex. The protocol-led, target-driven approach incorporated a small RCT of therapy algorithms to estimate their relative efficacy for the potential large-scale trial of glucose control and CVD in primary care, and an observational design was used to compare outcomes using this approach with standard care within this study. Separate large randomised controlled outcome studies specifically addressing each of the objectives would have been preferred and would have provided valid conclusions on the CVS benefits of metformin versus rosiglitazone, the relative merit of basal or prandial glucose lowering, the advantages and difficulties of earlier insulin use versus OHA, the efficacy of patient management schedules and targets in chronic disease care, the benefits of HBGM versus no monitoring and the different education models for use in T2DM. Improved methodologies tailored to individual specific objectives would then have been possible.

An RCT comparison of participants versus non-participants was needed to prove superiority of the novel general practice approach with patient management plans, therapy algorithms and provision of targets versus standard care and the observational study used was insufficient for this purpose. Only indirect and speculative conclusions can thus be drawn. Equally much larger powered outcome RCT for the other questions were needed to provide definitive and valid conclusions. These multiple, large distinct RCT studies were beyond the scope of this D Phil project requiring a large research team and many years to complete. The design used in this study enabled a broad exploration of the issues, provided important information about trial acceptability, patient recruitment and retention, and important data to inform the methodological design, scale and conduct of future, large-scale, well-designed, definitive RCTs addressing some of the greatest current challenges in T2DM care.

The glucose study was limited to a self-selected and atypical group of highly motivated patients with a relatively short duration of diabetes and current therapy with diet or oral monotherapy alone. Generalisability of the results is thus limited. Non-random selection of general practices might have produced selection bias with potentially higher standards of care in recruited centres as a result of their declared interest. The small number of practices and their confined locality within Oxfordshire and Buckinghamshire might also limit generalisability to practices in other regions with contrasting age, social or economic profiles. Equally the study population comprising predominantly Caucasian individuals, might differ substantially from other areas. Broader inclusion criteria particularly for age and therapy use would have enhanced patient recruitment but made it difficult to transfer to monotherapy to compare primary therapies. This lack of generalisability has important implications for the feasibility of the large-scale studies to follow and clearly design changes are crucial to recruit large numbers of patients. The reasons for poor response and low retention in the study need further analysis to determine the changes needed for future large-scale trials to operate successfully. Further qualitative research based on the early findings in this study is thus required.

T2DM prevalence in practices was unexpectedly low most likely indicating incomplete identification and registration of patients. Screening and a thorough review of the notes may have enhanced yield but was not practical with the time constraints of the study. Recruitment was difficult and yield of patients willing to participate also low. The size of the study was thus small with no power to detect changes in the major endpoints and indeed only 'trends' in glucose lowering, biochemical measures and CVS risk were determined. Many of these non-significant results may have reached significance with a larger study population and indeed the small sample size means that effects due to a lack of real difference are indistinguishable from those caused by lack of power where a real difference does exist. Discussion about the increased frequency of study clinics, therapy intensification and earlier

insulin use prior to recruitment provided useful data regarding more widespread implementation of the programme but may have deterred participation. A more gradual exploration of these issues with increased education after study onset could have enhanced participation but equally may have led to increased patient dropout.

Methodological weaknesses in the study design were also apparent. Significant baseline differences in HbA_{1c} and FPG values between therapies occurred as a result of failure to include these variables in the minimisation criteria at randomisation and necessitated adjustment in subsequent analyses. The elevated baseline triglyceride levels in the glipizide groups most likely reflected the increased glucose values in these patients. Glucose should be included in the minimisation programme for the large scale trials.

The therapy sequences adopted in this protocol were created before publication of NICE guidance and reflected the need to explore the feasibility of insulin initiation in primary care and to compare the CVS benefits of potential first line agents over and above the effect of their glucose lowering properties. Pure comparison of primary therapies was accomplished by addition of similar second line agents but was not possible for sequence F where acarbose substitution was used to avoid sulphonylurea duplication. Simplification of therapy sequences and use of two OHA agents prior to insulin in further studies would be recommended to enhance acceptability and reduce withdrawals. The agents used within the sequences are not standard first-line therapies in general practice and further evaluation of the benefits of basal and prandial therapy combinations versus standardised regimens are needed to define the ideal sequence for use with the approach in practice.

Contrasting dose regimens, pharmacological properties and tolerability of agents complicated the algorithm operation. Problems included delayed glucose lowering with rosiglitazone, gastrointestinal side effects of metformin necessitating slow titration and calculation of equivalent OHA doses at baseline to avoid undue hypo or hyperglycaemia at baseline. Potential improvements would include inclusion of the gating calculation on case report forms and an explicit statement of the decisions and action taken by practice nurses as a result of the calculation for ease of analysis.

Integration of practice diabetes systems with the glucose optimisation strategies is needed in future research. Annual reviews were not included in this study as a result of its short time-scale but would be vital in larger scale trials to ensure comprehensive coverage of the clinical tasks and GMS points for T2DM care in practices. This would also potentially enhance recruitment.

This study used validated quality of life and resource utilisation questionnaires to evaluate the effect of glucose optimisation on patients. Study specific scales could have provided data regarding particular protocols but piloting and validation of these instruments was not possible within the timeframe of this study. The most widely accepted, concise and relevant scales were chosen for use in the study. All had been validated specifically with diabetic patients. The wellbeing and treatment satisfaction measures were particularly valuable enabling changes in quality of life and satisfaction to be explored with each therapy change. This enabled satisfaction with insulin versus oral agents to be compared and popularity of individual therapies gauged, providing useful data for healthcare delivery. The health thermometer and resource utilisation scales were those used in the UKPDS cost-effectiveness analyses. Specific tools were used to obtain general feedback from patients about the study at closeout and open-ended sections were used to gauge general views. Many authors have explored the estimation of sample size requirements for reliability studies using these questionnaire tools (Kline, 1986) in relation to the bounds of the acceptable confidence interval levels (Gore 1981; Armitage 1987; Streiner 1989) and generally a minimum sample size of 200 patients for analysis is recommended. The sample size in this study is, once again, too small to provide valid conclusions for questionnaire items but highlights important areas of relevance for subsequent large-scale work. Significant findings may be present despite non-statistically significant results in the behavioural components of this study had a larger sample had been recruited.

Food diaries provided a detailed insight into the dietary habits of patients and were used to provide individualised lifestyle advice. The dietetic role was fulfilled by practice nurses using standardised leaflets and targeted feedback. Many patients had not received prior dietary advice and all welcomed this evaluation. Formal dietetic input and group exercise provision might have been advantageous in the study in order to reduce weight gain with OHA combinations and insulin.

Guidelines for hypertension and hyperlipidaemia and target levels were included in the resource pack to enable practice nurses to optimally manage all CVS risk factors. Direct prompts were not provided if BP or lipid levels were outside target ranges but outcomes were audited. Randomised addition of antihypertensive and lipid agents could have provided additional information but was deemed untenable as a result of the protocol complexity and availability of existing hypertension trials. The study was completed before publication of the UKPDS risk engine and used Joint Heart guidance for cardiovascular risk calculation The UKPDS risk engine, including a measure of blood glucose control might have provided improved results.

Measures of adherence in the study were entirely subjective and based on the self-care questionnaire scale. Duplicate items relating to each variable were omitted to provide a concise scale. Subjective

reports of dietary and glucose monitoring adherence were checked against food diaries and memory meters. Objective measures of adherence including tablet counts and electronic pill-counting bottles would have provided more accurate results but were not feasible with the financial constraints on the study.

Seven point glucose profiles were selected to provide detailed basal and prandial measures from a known morning fasting glucose value. Patient performance with the two-hour timers was good with most patients providing one weekday and one weekend profile. Excess profiles were frequently taken by patients to assist their own education and self-management skills. Difficulties arose with changes in time zones with business travel, shift work and atypical mealtimes, omission of meals and shortened days arising from an early sleep pattern with less than two-hours after the post evening meal measure. These situations were documented in manual glucose diaries and only six measures were often included.

Quality assurance for biochemical measures was tested monthly. Monthly HbA_{1c} measures were taken despite the 8-12 week turnaround to gauge more precisely trends in glucose lowering with the frequent therapy changes. Although basal and post-prandial glucose were targeted simultaneously to attain maximal glucose optimisation addition of therapies and dose titration occurred monthly to enable identification of side effects with individual agents.

Forced titration rather than gating was used for the titration of rosiglitazone as a result of its delayed pharmacological onset of action. Despite this adjustment to the protocol some patients still experienced hyperglycaemia on moving from biguanide or sulphonylurea to rosiglitazone at baseline and required early isophane to control basal glucose values. Many patients were unhappy with the speed of protocol titrations and requested delays before therapy change or insulin addition. Delay was resisted wherever possible to maintain the obligatory protocol structure but occasionally an additional week of glucose measures was considered to maintain patient involvement in the study.

Statistical significance was difficult to determine in this small, feasibility project. It was not possible to distinguish between a true lack of difference in results or insufficient power of the study to detect a difference where p values were greater than 0.05. Equally although significance is assumed for P values below 0.05 these results may obviously arise occasionally as a result of multiple tests. This study ofen used multiple statistical comparison tests or analyses where in larger scale trials only one would be preferable. An example of this is weight where a non-normal distribution was shown in the small sample size of the study but where normally it is known to be normally distributed eg UKPDS

Both parametric and non-parametric tests are included in this instance. Generally AUC and IAUC would be preferred for all repeated measures analyses in larger studies and ITT for large RCT data.

9.3. Relationship to other studies

This study uses much tighter criteria for glucose control than those selected in other studies. The strong correlation between degree of hyperglycaemia and diabetes complications in UKPDS and the lack of an effect threshold indicated that the best possible glucose levels should be sought in practice. Basal and prandial glucose targets of <6.0mmol and <8.0mmol, the upper limit of normal physiological values, were selected as the goals for glucose optimisation in this study.

Similar glucose lowering to that achieved in UKPDS was seen despite a much lower baseline HbA_{1c} demonstrating the potential benefits of earlier use of OHAs and insulin and indicating that the goal of normoglycaemia is likely to be tenable within T2DM populations. Pure comparison of first-line agents was maintained as far as possible by randomisation to similar second-line agents overcoming the drug crossover and substitution in UKPDS. Considerable overlap in treatments given to the two groups occurred in UKPDS with 702 of 1138 patients in the conventional therapy arm eventually receiving sulphonylurea, insulin or metformin.

Most existing studies of glucose optimisation have focused on fasting glucose or HbA_{1c} values and very few have examined effects of combining agents to simultaneously target both fasting and postprandial levels. The downloaded patient glucometer records in this study appear to be unique and provide a more detailed record of fasting and prandial glucose adjustment than in other studies.

Head to head comparison of six distinct therapeutic sequences is unusual and contrasts with existing RCTs where individual therapies are generally compared with each other or placebo. The primary comparison between biguanide, TZD and sulphonylurea was chosen to enable comparison of three major drug classes and to compare relative benefits of TZD versus biguanide over and above their glucose lowering effects on CVS outcomes in a major trial. UKPDS showed that metformin was advantageous in overweight patients, reducing weight gain, hypoglycaemia and macrovascular risk (32% risk reduction, p=0.002) more than sulphonylurea or insulin. This study structure provides a feasibility assessment for a 3x2 factorial RCT comparing biguanide versus TZD, and meglitinide versus rapid acting insulin. Placebo use would be deemed unethical in this study as a result of the proven benefits of existing diabetes therapies.

Glucose optimisation was achieved in this study without incurring significant hypoglycaemia or serious adverse events, and without negatively impacting on quality of life, adherence or treatment satisfaction in patients. These are the commonest arguments against glucose optimisation in practice but were not substantiated by this research.

This study does not include a randomised cardiovascular risk management trial as with many others. UKPDS compared the effects of two levels of blood pressure on T2DM complications and smaller studies have examined efficacy of different antihypertensive agents. Multifactorial risk intervention remains an essential component of T2DM care and CVS risk modification with standardised national guidelines was emphasised throughout this project. Blood pressure was monitored monthly, lipids measured annually and BHS and lipid guidance issued to practices. Randomisation to lipid and blood pressure agents was considered and could have provided useful additional information but protocol complexity and the availability of existing hypertension trials made this unfeasible.

Many of the barriers to improving diabetes care identified in this research are the same as those in a GP postal survey by Agarwal (2002) in which patients' unwillingness to make behavioural changes or attend frequent clinics, non-adherence with medical regimes, lack of time and lack of space within primary care centres were key determinants.

9.4 Discussion of Principal Results

9.4.1 Participation of patients and practices

Overall participation of patients and practices in this study was low indicating that modification is required before large-scale RCT outcome trials may be undertaken. Randomisation, use of newer therapies, higher visit frequency and involvement of personnel separate to the general practice team are likely to have reduced participation. Recruitment to an integrated programme of glucose control in general practice operated by the primary care team with less intense monitoring, slower therapy titrations, fewer clinic visits and use of two oral agents prior to insulin would be expected to yield better results. Determination of the principal barrier to recruitment was useful to capture patients' participation decisions in this study but more detailed exploration with large qualitative studies and detailed interviewing techniques is now needed.

Poor differentiation between T1DM and T2DM patients on practice computers complicated the identification of eligible patients and specific read code use is recommended to enhance the accuracy of clinical care and future research. Systems of registration and recall were noted to be incomplete

with most practices still relying on patient attendance rather than prompting for diabetes reviews. Identification of inclusion and exclusion criteria from computer records was difficult and manual notes and laboratory results were frequently searched to provide accurate information.

The choice of inclusion and exclusion criteria in the study were tailored to the design of larger therapeutic outcome RCT and were not suited to the comparison of the novel algorithmic approach versus standard care where more generalised criteria, wider age ranges and inclusion of patients on multiple OHA therapies would be preferable. Age criteria were selected to ease identification of T2DM, maximise number of clinical endpoints and exclude elderly patients who may be incapable of performing trial tasks. Therapy criteria were chosen to enable conversion to monotherapy and comparison of primary therapies without marked hyperglycaemia occurring. Contraindications to study medication were selected to enhance trial safety. Distinct future studies with methodologies tailored to individual objectives and distinct inclusion/exclusion criteria would be beneficial.

Adaptation of algorithms and monitoring techniques for elderly patients and those on combination OHAs would be necessary for large RCT comparison trials of the standard versus novel approach. These trials would provide definitive conclusions on the optimal approach to T2DM care within the vast majority of T2DM patients rather than a small selected subgroup of middle-aged patients on monotherapy alone. Translation of educational materials is needed for ethnic minority groups.

The high number of patient withdrawals in this project most likely reflects the programme intensity. Monthly visits, rapid OHA titration, frequent questionnaires and use of only one oral agent prior to insulin was necessary to check algorithm operation and explore the effects of increased therapy use but would not be needed in practice now that the safety of this approach has been determined on a small-scale. Three monthly visits, use of two OHA prior to insulin and flexible titration schedules for those with medication side-effects would now be possible.

9.4.2 Characteristics of Recruited Patients

A relatively low mean baseline HbA_{1c} was seen in all patients in this study compared to the UK national average indicating a higher standard of local diabetes care and lower potential for glucose reduction in this study compared with other UK geographical areas. Baseline glucose targets still exceeded UKPDS, NICE, AACE and EDPG guidance, however, supporting the CODE-2 data in which 64% of patients on metformin and 66% on sulphonylurea monotherapy exceeded HbA_{1c} targets >6.5% (CODE-2 group,1999). The need for polypharmacy with poor glycaemic control had not been accepted by study practices, with one third of poorly controlled patients at baseline still

treated with diet alone at mean duration 3-4 years. Equally over one third of patients were using sulphonylurea alone at baseline despite the proven additional benefits of metformin. These findings suggest that provision of EBM guidance is not sufficient to alter practice. Discrepancies between documented and actual BP and lipids at baseline were seen and prevalence of T2DM complications was lower than predicted, most likely reflecting recording errors. The high mean baseline BMI of patients highlighted the greater degree of obesity in T2DM groups.

Use of the ADS scale in T2DM patients may be useful to facilitate education and self-care skills. Increased awareness of the likely worsening of their illness may enhance the perceived importance of glucose, BP and lipid optimisation but may be associated with increased upset and concern over diabetes as seen in recruited patients.

9.4.3 Therapy Use

The need for polypharmacy in T2DM was exemplified by the rapid increase in therapies in the study despite the short duration of disease and relatively good control in patients. 51% of patients required 3 therapies, 34% 2 and 15% 1 therapy at one year, with higher proportions expected in those with longer disease durations, poorer glycaemic control and greater weight. Most patients were taking additional therapies for hypertension, hyperlipidaemia and cardiovascular protection. The resource implications of this data are enormous, necessitating greatly enhanced drug budgets and funding in practice.

The ability to achieve glucose targets irrespective of the particular pharmacological agents chosen was important, permitting regime flexibility with tolerability issues. An overall trend to fewer therapies and lower doses in the metformin versus other groups was seen reflecting the lower baseline glucose values in this group but perhaps too confirming its benefits as a first-line agent. Larger scale studies are needed to confirm these results. Acarbose was poorly tolerated as a result of gastrointestinal side-effects. No patients were sustained on maximal doses of prandial therapies.

Increased insulin use at an earlier stage in T2DM and initiation within primary care was clearly feasible but once again with enormous resource implications for practices, requiring increased staff training and support, and enhanced consultation lengths for skills transfer. The training programme, consultation times and additional support needed in this study would be helpful for the planning and design of future trials and policy formulation.

Chi-square analyses were used to provide a contrast between the proportions of patients on one, two or three therapies at 0, 6 and 12 months in this study but the AUC and IAUC analyses more accurately reflect exposure to therapies with repeated measures over time. These analyses are shown for each of the variables measured at monthly intervals throughout the study.

9.4.4 Adherence

Complex interventions based on theoretical frameworks were not incorporated in this study and only simple techniques to enhance adherence were used. The patients perspective was obtained where issues of non-adherence had arisen, active involvement in the dialogue and patient-centredness were encouraged and efforts to locate the problem and renegotiate solutions made. Simple prompts and practical devices such as two-hour timers were provided to assist with non-adherence and patient empowerment through the provision of therapeutic algorithms, insulin adjustment schedules and knowledge of glucose targets was encouraged. These processes were limited as a result of the trial nature of the study but could be greatly expanded within an applied general practice programme.

Food diary data revealed a close correlation between the fat, CHD and energy content of recruited patients compared to the standard UK population. No significant difference between therapy groups at baseline were seen. Decreased adherence with dietary recommendations with time was seen in study patients consistent with diet adherence literature. The lower adherence with high fibre foods in the metformin arm possibly reflects increased gastrointestinal disturbances with this therapy.

Exercise adherence was poor throughout this study with less than a quarter of patients taking the recommended levels of exercise despite monthly reminders of this guidance. This finding highlights the need for behavioural and strategic measures to promote exercise in the population and research to clarify effectiveness of exercise interventions (prescription schemes and group programmes) on adherence in T2DM patients.

Adherence with HBGM was unexpectedly high indicating that PPG surveillance is clearly feasible and suggests that HBGM is a powerful tool for patient education and empowerment. Further large-scale RCT of monitoring versus no-monitoring and fasting with prandial monitoring versus fasting alone are needed to confirm these results.

9.4.5 Therapeutic Effects

The reduction in HbA_{1c} attained in this study was consistent with that achieved in UKPDS and occurred irrespective of the agents used. Glucose optimisation was clearly feasible in this selected subgroup of T2DM patients in primary care with the majority attaining the more intensive targets of recent guidelines. Patients who failed to meet targets were generally those who had poor control at baseline, lower adherence with lifestyle and therapy regimes and greater BMI. The tolerability of therapeutic agents and delayed glucose lowering with rosiglitazone were highlighted. Extrapolation of algorithms to patients already treated with combination therapies and insulin, and large-scale clinical outcome trials of therapy algorithms are now needed.

This study did not have the power to determine changes in cardiac risk reduction with glucose lowering but a tendency towards decreased cardiac risk was observed, confirming the findings of UKPDS. Surrogate biochemical markers of cardiac risk were not significantly altered by glucose lowering but again this may reflect the small size and lack of power to detect a difference. A large-scale study of glucose optimisation and CVS risk reduction is needed to clarify these effects.

The protocol-driven, treat-to-target approach used for glucose optimisation in the study produced better outcomes than with guideline provision alone. Blood pressure and lipids changed little during the year and outcomes in routine practice were largely unchanged despite availability of evidence and guidelines. This finding implies that methods of changing clinical practice need to be more controlled with clear targets and regular feedback to assure results are attained.

9.5 Implications of this research for clinicians and policymakers

9.5.1 The need for change

This thesis reviews the evidence suggesting that T2DM is now a substantial global health concern of epidemic proportions. The morbidity and mortality from complications are enormous and healthcare expenditure is rising rapidly necessitating an urgent need for action. A wealth of research evidence exists indicating best management and emphasising the importance of reducing complications through improved blood pressure, lipid, CVS modification and glucose control. The necessity to attain and maintain near normoglycaemia, to evaluate the CVS protective effects of different therapeutic agents, to determine the acceptability of intensive management policies and to deliver evidence-based best practice care are now paramount. Development of effective protocols for

fasting and postprandial glucose, CVS risk and lifestyle modification including smoking cessation, diet and exercise adherence are required.

9.5.2 The potential of primary care

The potential for improvements in delivery of care and health outcomes for people with T2DM is great and primary care provides a unique positive environment for these tasks to be undertaken. Its emphasis on the provision of personal, comprehensive and continuing care for individuals and their families in local, convenient settings with open access, 24-hour cover and free healthcare delivery is well-suited to the prevention, early identification, surveillance and management of chronic disease.

The infrastructure and organisation of services in primary care is also suited to T2DM management. The availability of a multidisciplinary team including nurse, podiatrist and dietitian provides a structure for the screening of complications and referral to the wide range of specialist agencies in community or hospital sectors enhances care provision. Equally the personal relationship established between patients and healthcare personnel in general practice as a result of their continuing care is ideal for the provision of successful education programmes and enhanced self-care activities. The primary care team are often more aware of family circumstances and effects that may impact on T2DM than hospital workers and indeed family support or encouragement can be summoned to improve self-care where needed.

Primary care use of information technology is currently more advanced than that in the secondary care sector and is well suited to prevention and surveillance, enabling accurate registration, recall and review of patients.

9.5.3 Positive pressures for change

The current political drive is positive for people with T2DM. The NSF DM publication emphasising quality standards and the new GMS contract for general practice with increased payment for the delivery of quality indicators provides resources and political persuasion for primary care units to improve the structure, provision and outcomes of T2DM care. This research together with guidance such as NICE provides the framework by which these quality indicators can now be met.

Current patient and consumer pressure is also positive towards change. The Audit Commission highlighted definitively for patients current shortfalls in healthcare delivery and target achievement

evident in the research literature (Pierce, UKPDS, Farooqi, Khunti) increasing their demand for improved T2DM care within a primary care setting.

Finally the availability of new technologies including insulin pen devices, needle free injections, newer OHA and insulin agents provides positive pressure and capability for improved glucose and healthcare outcomes in T2DM.

9.5.4 Potential barriers to change

The barriers to improved T2DM control commonly cited by the research literature and health professionals involve patient factors, practice issues and resources. Poor patient knowledge and education decrease motivation towards self-care skills, training and knowledge of practice nurses is often limited in general practice, a shortage of hospital DSNs limits community support to practices and consultation lengths and time considerations in primary care are prohibitive towards insulin initiation and key skills. These barriers were substantiated by this research and overcome by improved training of the nurses, provision of detailed patient education materials and enhanced time for clinics. Other barriers to glucose optimisation including hypoglycaemia, weight gain, adverse events, reduced patient quality of life and therapy satisfaction with polypharmacy were not substantiated.

One of the major barriers to improving T2DM control identified by this study was patient and practice participation. Potential solutions to these problems are examined later in this section but the need for large-scale studies and qualitative research in this area is paramount.

9.5.5 Implications of this study

The results of this study are important for the planning, design and conduct of future large-scale therapeutic RCT in T2DM, for the conduct of a large RCT of algorithm-driven versus standard care and for the provision of quality care for people with T2DM. Nurse-led, protocol driven, obligatory, treat to target algorithms appeared in this small study to be safe and effective for general practice use and could achieve superior results compared to standard practice care. OHA intensification, insulin initiation and dose adjustment were accomplished with appropriate training and support for practice nurses, glucose optimisation was attained without incurring severe hypoglycaemia episodes or SAE and no negative impact on wellbeing, health perception or therapy satisfaction was seen. The degree of fasting and prandial glucose lowering attained in the study already reached newest recommendations and occurred irrespective of the particular therapy algorithms selected. Adherence

was maintained despite earlier combination OHA and insulin use, with increased education and support for patients.

Further large-scale research using these concepts is required to substantiate the findings and confirm that protracted periods with diet or monotherapy are no longer justifiable in T2DM management. Patients' expectations for increasing therapy with time and insulin use to counteract the progressive hyperglycaemia characteristic of beta-cell dysfunction in T2DM must be set earlier in the disease course. The conditions enabling insulin initiation and adjustment in this study should be tested in a larger study and compared to the best available educational protocols. The optimal method should be disseminated so that insulin management in primary care is the norm and lengthy delays awaiting overburdened secondary care services limiting the efficiency of glucose optimisation can be avoided.

The need for CVS risk modification in T2DM is already clear and the relative benefits of different therapeutic agents on CVS risk must now be determined in large-scale RCT outcome trials.Potential benefits of metformin as first line therapy in T2DM care, with less weight gain and reduced need for polypharmacy were seen in this study but no significant differences between biguanide and TZD agents on surrogate biochemical CVD risk markers were observed. It is not possible to say whether this lack of observed difference was true or due only to a small sample size in the study. Large-scale outcome trials of metformin versus TZD agents are thus needed. The poor tolerability of acarbose and difficulty using insulin after one oral agent seen in this study suggests that a simplified protocol comparing only biguanide versus TZD agents may be feasible. This could be structured as a head to head comparison or 2x2 factorial randomisation with a comparison of two second line oral agents eg sulphonylureas and meglitinides.

This study suggests that therapeutic algorithms, titration schedules, clear targets and defined action points may improve the quality of care and significantly enhance chronic disease health outcomes, and large-scale RCTs of protocol-driven management of T2DM are now needed to prove superiority of this approach versus standard care. Professional adherence to guidelines can be problematical as seen in this study by the poorer adherence with blood pressure and lipid management compared to glucose. Standardised guidelines for CVS risk modification were rarely accessed whereas obligatory algorithms, titrations, targets and protocol checks by the research centre produced improved results. The value of other systems to enforce protocol adherence including audit, quality payments, clinical governance and computerised decision support systems should also be explored.

Barriers to intensification of therapy, glucose and CVS risk modification in primary care should be addressed. The recruitment analysis in this study suggests a need for T2DM clinics to be accessible

outside of working hours and highlights the need for improved education to overcome resistance to therapy change. The high withdrawal rate in the study emphasises the need for increased education, exposure and novel delivery techniques to counteract resistance to insulin use and need for careful dose titration and newer oral agents with fewer side effects and increased tolerability. Further large-scale qualitative studies and detailed interviews are needed to explore other potential barriers.

This study suggests that empowerment of patients is possible with increased education, glucose monitoring and open access to planned therapy regimes. No patients, even those who were already monitoring their glucose values, were aware of the targets for glucose control at the onset of this study and few knew how best to adjust lifestyle and therapy doses to achieve optimal results yet by one year all patients within this small study were aware of fasting and prandial glucose targets, could give reasons for high and low values, and most were able to adjust insulin doses. Further research to substantiate these findings is needed.

T2DM is a challenging management problem for both patients and practice staff. The need for lifestyle modification, polypharmacy, CVS risk modication and HBGM is arduous and support is needed wherever possible. Registration and recall systems have been shown already to be essential for comprehensive T2DM care delivery. Clearly defined glucose, blood pressure and lipid targets and EBM algorithms with clear action points and therapy titration schedules could help to achieve optimal control. Clinical governance to enhance performance and financial incentives to encourage practices to meet quality targets may also be advantageous. The development of computerised decision support systems to enforce clinician adherence to protocols and prompt correct actions in the consultation, combination agents to improve adherence and targeted behaviour modification to enhance disease management skills may also be helpful. The optimal delivery of education of patients and clinicians to overcome resistance to therapy change, insulin use and improved T2DM care must be determined. Creation of general practitioner intermediate T2DM care leads and insulin liaison nurses within each PCT may facilitate information transfer between secondary and primary care, ensure dissemination of new ideas and quality practice and provide additional support needed to achieve optimal goals for T2DM care in general practice.

Large-scale studies are needed to substantiate these research findings and encourage clinicians and policymakers to focus on polypharmacy, CVS risk modification and earlier insulin use in T2DM management. Dissemination of insulin skills to practice nurses and management of insulin regimens in primary care is needed. Combination pharmaceutical preparations and alternate delivery modes for insulin may be beneficial to assist adherence. Group support for patients to encourage adherence

to lifestyle and therapy measures may also be helpful. These aspects could readily be incorporated into subsequent trials.

9.6 Unanswered questions and future research

Extensive modification of this approach is required before future large-scale research is possible. The key question in designing large-scale follow-on RCT and implementing this approach in general practice is how to maximise patient and practice participation and retention. Extension of inclusion criteria to include broader age groups, patients on multiple oral agents and insulin, wider HbA_{1c} criteria and concomitant illness would enhance patient yield in practices. Integration and delivery of the programme as part of routine practice care by patients' own general practitioners rather than a RCT format co-ordinated by the University would also be expected to enhance recruitment. Provision of clinics at three monthly intervals, accessible outside of working hours would facilitate participation in working age groups. Development of a national or regional register for diabetes for use with audit, research and clinical care would facilitate identification of eligible research subjects and enhance recruitment processes. Finally increased education to improve the awareness of patients towards the need for glucose and CVS risk factor modification, polypharmacy and insulin use, and to encourage knowledge of target values at diagnosis of T2DM may be advantageous enhancing motivation to participate in similar studies. Fears surrounding insulin use appear still to be very real for most patients and exposure to information, pen devices and trial injection at an early stage in the disease course before insulin use is essential might help prevent delays and encourage participation. Integration of standard T2DM practice care tasks into the study, provision of data in MAAG format matching GMS quality criteria, financial incentives for improvement and additional funding of key personnel may enhance practice participation. Creation of a T2DM intermediate PCT lead and insulin liaison nurse may also be advantageous in rolling-out the approach.

A second key issue in the design of subsequent large-scale studies is how best to attain and maintain optimal patient adherence to multiple risk factor interventions and polypharmacy use throughout the course of a trial or chronic disease. Further research investigating the effectiveness of behavioural and motivational strategies in promoting adherence to diet, lifestyle, monitoring, glucose and CVS risk factor therapies is needed and the optimal mode of delivery of education and skills should be determined. Elucidation of the optimal sequence of therapies to achieve targets and formulation of safe OHA combinations and alternative insulin delivery modes remain central.

A large RCT of glucose and CVS risk factor modification comparing the protocol-led, target-driven, approach versus standard general practice care should be undertaken in a broader study population

using NICE therapeutic guidance to gauge the improvements possible. CVS risk factor management should be driven by obligatory titration schedules in the same way as glucose in order to gauge the degree of polypharmacy and psychosocial consequences for patients. Detailed qualitative interviews to explore adherence and resistance issues should be undertaken and group or individual educational strategies trialled to define the optimal model of care for this chronic disease. Computerised T2DM decision support systems for glucose and CVS risk modification rather than CRF forms may be helpful and more convenient for use in general practice and may facilitate target driven obligatory titration of therapies. Cost-effectiveness analyses should be undertaken in parallel with the larger-scale studies to provide an estimate of the resources required to roll-out the programme nationally and internationally. Extrapolation of these principles to management of other chronic diseases in primary care will then be possible.

The sequence of therapies included in the CVS trial of biguanide versus TZD should be simplified before conducting a large-scale RCT. A revised protocol using either a head to head comparison or 2x2 factorial randomisation could be used, perhaps adding a comparison of second-line therapies such as sulphonylurea versus meglitinides in addition to the primary comparison. This would enable use of humalog only after two oral agents. Use of glargine insulin now that it is available would be advantageous to optimise control and medication adherence. A clinical outcome trial with hard CVD endpoints would be proposed in addition to analysis of surrogate biochemical measures and cardiac risk. Use of the network of UK research general practices who are familiar with the conduct of large RCT may facilitate recruitment and conduct of the trial. Computerised data forms and decision systems would negate the need for research staff to be on site to verify therapy progression and would facilitate transfer of information by email or fax to the study co-ordinating centre.

Chapter 10: Conclusions

10.1 Summary of principal conclusions

10.1.1. Principal findings:

This small study demonstrates that glucose optimisation in T2DM may be successfully achieved in a primary care setting using a nurse-led, protocol-driven, obligatory treat to target approach.

Improved fasting and post-prandial glucose was attained without impacting on QoL, adherence or therapy satisfaction in this study but larger-scale studies are needed to substantiate this finding. No severe hypoglycaemia episodes or serious adverse events occurred.

The approach with patient management plans, clear targets and obligatory dose titration algorithms where glucose targets were exceeded appeared to achieve better results than standardised guidelines used with the other CVS risk factors. Further randomised studies of these findings are needed.

Whilst a randomised study is needed to prove superiority a trend towards improved biochemical and metabolic outcomes was seen in study patients compared to those remaining in standard practice care. CVD risk indices were reduced and no new microvascular complications occurred in the year.

Insulin initiation and adjustment were successfully achieved in this study with a detailed programme of training and support for practice nurses. Titration schedules for OHAs and insulin were shown to be safe, effective and acceptable to patients.

Potential barriers to achieving optimal T2DM care in practice were explored. Training issues, time constraints, technological considerations and patient factors may underly some of the resistance to therapy change, insulin use and intensive T2DM management in primary care.

10.1.2. Practice and patient participation:

Only 7/20 (35%) practices and 60/345 (17%) eligible patients agreed to participate in the study. Practice participation was limited primarily by time constraints and structural considerations (room availability) whilst patient recruitment was limited by work and time commitments, resistance to therapy changes and insulin use. Further qualitative research is needed to explore these issues.

Baseline characteristics of recruited and non-recruited patients were similar indicating that recruited patients were likely to be representative of the larger T2DM population within practices.

Patients interested in taking part in the study appeared to be more upset and uncertain about their diabetes, coping less well and more likely to consider their diabetes would worsen. They had a more external locus of glucose control than non-recruited patients when assessed using the ADS scale.

10.1.3. Therapy use:

The mean number of therapies required to attain normoglycaemia in T2DM patients in this small study increased from 0.7 at baseline to 2.4 at one year.

51% patients required three therapies, 34% two therapies and 15% monotherapy to achieve fasting and prandial glucose targets at one year. Fewer therapies were required in the metformin compared to rosiglitazone or glipizide arms in this study.

9 (15%) patients successfully commenced isophane, 1 (2%) humalog and 15 (25%) both insulins, in this programme. Patients in the glipizide arm had significantly more isophane ($p=0.03$) and humalog ($p=0.008$) use than other therapy sequences.

10.1.4. Acceptability, Adherence and Safety:

Adherence to diet, exercise, glucose monitoring and therapy was high and was maintained with time from randomisation despite therapy increases and insulin use.

30% patients always adhered to dietary advice, 60% usually adhered and 10% sometimes adhered. 20-30% patients always adhered to exercise advice, 30% usually adhered, 30% sometimes adhered and 10-15% never adhered using the Activities of Self-Care Diabetes scale.

Adherence to basal, prandial and insulin therapy was 60%, 55% and 51% with ITT analyses and 88%, 88% and 92% with VC analyses at one year respectively. No significant differences between therapy groups were seen.

The small sample of practices and patients who participated in the study welcomed this approach to glucose control. Patient wellbeing, QoL and health perception was sustained at a high level despite increased polypharmacy and insulin use.

No significant decline in health perception (p=0.30) or treatment satisfaction (p=0.37) occurred in the study despite earlier use of OHA combinations and insulin, reflecting either a true result or lack of power in the study to detect a significant change.

No serious adverse events and no episodes of severe hypoglycaemia occurred. Idiosyncratic effects of rosiglitazone on hepatotoxicity and haemodilution were not observed.

63 minor adverse events occurred and 31 of these were perceived to relate to study medication. GI side effects with metformin, arthralgia and ankle oedema with rosiglitazone, weight gain and symptoms of hyperglycaemia at study onset were the commonest reported events.

10.1.5. Glucose control:

A mean overall HbA_{1c} reduction of 0.8 ± 1.0% (p<0.0001) was attained with a reduction of 1.2% in protocol-adherent patients irrespective of the therapeutic agents used. 95% of protocol-adherent patients and 72% of all patients achieved HbA_{1c} targets <7.0%. 83% of protocol-adherent patients and 62% of all patients achieved the more intensive target HbA_{1c} <6.5%.

An overall mean reduction in fasting glucose values of 1.5mmol/L (p<0.0001) was attained with a reduction of 2.4mmol/L in protocol-adherent patients irrespective of the therapies used. 61% of protocol-adherent and 45% of all patients attained intensive FPG targets <6mmol/L at 1 year.

A significant overall mean reduction in post-prandial glucose of 3.4mmol/L and 3.7mmol/L in protocol-adherent patients was attained irrespective of the therapies used. The proportion of patients achieving prandial glucose targets increased from 29% to 82% over one year.

Few episodes of significant hypoglycaemia resulted from glucose optimisation. Only four grade 2 and 1 grade 3 hypoglycaemia episode were reported during the year.

10.1.6. Body weight:

The overall mean weight gain in the study was 2.7kg with ITT analyses and 3.8kg in cohort patients. Significantly greater weight gain (p=0.006) occurred with glipizide and rosiglitazone therapy sequences than with metformin therapy sequences.

10.1.7. Blood pressure:

Overall mean SBP was reduced from 144mmHg to 139mmHg (p=0.05). The proportion of patients attaining SBP targets <135mmHg increased from 32% to 42% over the one year.

Overall mean DBP was significantly reduced from 84mmHg to 79mmHg (p=0.024). The proportion of patients attaining DBP targets <80mmHg increased from 40% to 60% over the one year.

10.1.8. Lipids:

No significant change in mean total cholesterol, LDL or HDL were seen. 63% of patients attained total cholesterol targets at one year compared to 48% at baseline. The respective figures for LDL and HDL were 63%, 57%, and 68%, 65%.

Overall mean triglyceride decreased significantly from 2.0 to 1.7mmol/L (p=0.001). The proportion of patients attaining TG targets increased from 59% to 63% at one year.

10.1.9. Cardiovascular risk:

Ten year CVS risk in study patients decreased from 19.3% to 16.8% over the year with both cohort and ITT analyses. Cerebrovascular risk decreased from 7.2% to 6.8% with ITT analyses. No significant differences between therapy groups occurred. No significant changes in CVS risk markers were observed during the year. This could reflect a lack of change or the lack of power of the study to detect small change in the variables.

10.2: Overview

This study demonstrates that glucose and cardiovascular risk factor optimisation in T2DM can be attained in a highly-selected group of patients in primary care using a nurse-led, protocol-driven, obligatory treat-to-target approach. Improved fasting and post-prandial glucose was attained with earlier combination OHA and insulin use and significant improvement in blood pressure, lipids and smoking were observed without negatively impacting on wellbeing, health perception, treatment satisfaction or adherence. Ten-year CVD and cerebrovascular risk indices were reduced over one year and no new microvascular complications occurred in recruited patients. Insulin initiation and adjustment were successfully achieved in practices with simple programmes of training and support for practice nurses and therapy titration schedules for OHA and insulin proved safe, effective and acceptable. No severe hypoglycaemia or serious adverse events were reported.

Patient recruitment and retention difficulties during this project indicate that extensive modification of the programme with provision of clinics outside working hours, reduced clinic frequency, use of two oral agents prior to insulin use, integration of GMS T2DM monitoring criteria, reduced HBGM and increased education for patients at diagnosis about the likely progression of the disease and need for insulin may be needed before further large-scale research is possible.

Definitive, large-scale, focussed, outcome RCTs with specific methodologies targeting each of the study objectives are needed for valid conclusions about the relative benefits of biguanides versus TZDs on CVD risk, the optimal agents for basal and prandial glucose control, the relative merits of early versus later insulin use, patient management schedules, HBGM, algorithms and targets. These conclusions will together provide research evidence to support the optimal management strategy and delivery of care for patients with T2DM. Further large-scale, qualitative research to explore reasons for withdrawal, non-participation and non-adherence is also needed.

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Appendices

Appendix 1: Summary Protocol

Background

Diabetes mellitus, often regarded as a "mild disease", is the fourth leading cause of death in developed countries with a two fold excess mortality and a two to four fold increased risk of heart disease and strokes. The number of people world wide with diabetes is predicted to double to over 220 million by the year 2010. The UK Prospective Diabetes Study (UKPDS) showed that 30% of those with type 2 diabetes (T2DM) developed clinical complications within ten years of diagnosis and that 59% of deaths were from cardiovascular disease (CVD). UKPDS analyses identified five potentially modifiable risk factors for CVD in these patients; raised LDL cholesterol, a low HDL cholesterol, hyperglycaemia, hypertension and smoking. UKPDS showed conclusively that improved glycaemic control reduced microvascular and macrovascular complications in T2DM. The challenge now is to determine how best to implement these findings in everyday practice and routinely achieve optimal glucose control in the face of declining beta-cell function in patients. In addition, there is a need to examine whether newer therapeutic agents can offer cardiovascular protection in addition to glucose lowering, as was seen with metformin in overweight UKPDS patients where the risk of diabetes-related death was reduced by 42% and myocardial infarction by 39%.

Study Design

Unlike the UKPDS, this study will use a protocol-driven, treat-to-target approach to glucose control and will specifically address basal and prandial components of glycaemic exposure. T2DM patients, aged 40 to 75 years with elevated HbA_{1c} levels (6.4% to10.0%) on treatment with diet alone or oral monotherapy, will be recruited from general practices in Oxfordshire and Buckinghamshire. All patients will receive specific advice concerning CVD risk factor management emphasising the need for appropriate management of blood glucose, blood pressure and lipid levels as well as the need for smoking cessation and aspirin therapy where indicated and will be taught how to undertake home blood glucose monitoring.

The aim in all subjects will be to achieve optimal glucose control with central randomisation to one of six distinct pharmacological treatment sequences based on three primary therapies. These agents target basal glucose and will comprise a biguanide, that reduces hepatic glucose output, a thiazolidinedione that increases insulin-sensitivity and a long-acting sulphonylurea that enhances endogenous insulin secretion. Primary therapies will be continued throughout the study. Following a two step dose titration all subjects will receive a second agent to primarily target prandial glucose levels. Those assigned to a biguanide or thiazolidinedione will receive either a short acting insulin analogue or meglitinide whilst those allocated initially to a sulphonylurea will receive either a short acting insulin analogue or an alpha-glucosidase inhibitor. FPG and PPG home blood glucose measurements will be used to adjust therapies aiming for as near normal values as possible. If glycaemic levels are elevated despite maximal therapy (FPG >6, PPG >8 mmol/L, HbA_{1c} >7%) long or short acting insulin will be added or substituted as appropriate.

Following a first visit to receive study information and assess eligibility for the study subjects will be seen at a recruitment visit to determine whether those who fulfil the inclusion and exclusion criteria are willing to join the study. Randomisation will be performed at one month. All subjects will be followed monthly for one year including, where possible, any that withdraw from study treatment. The study will operate according to GCP guidelines with data collected on standardised case report forms and quality of life assessed using validated questionnaires. Home glucose data will be downloaded from memory meters and a central laboratory will measure FPG, HbA_{1c}, total

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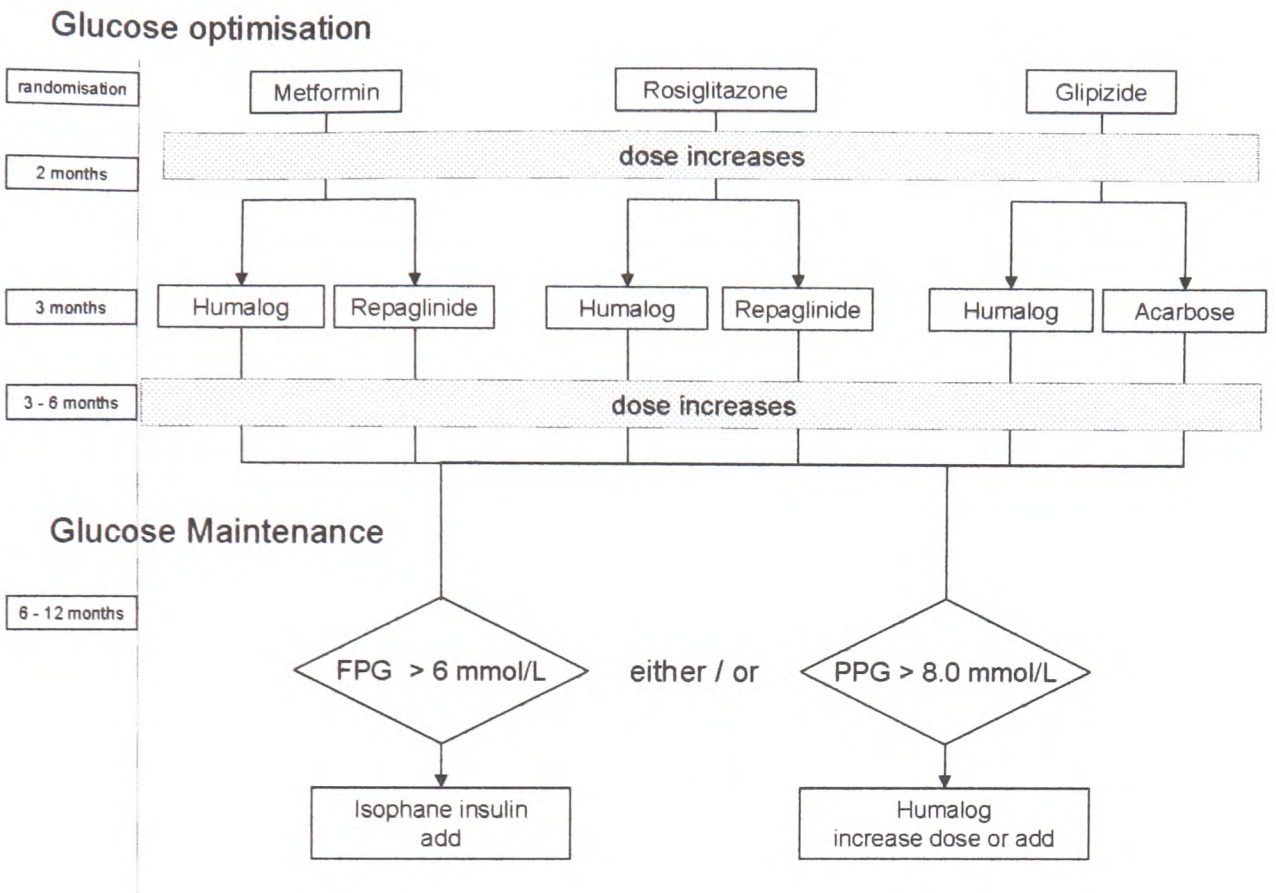
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cholesterol, HDL-C, LDL-C, triglyceride, ALT, creatinine and urinary albumin levels. The study will provide the basis for large-scale, practice-based, randomised clinical trials of glucose optimisation and CVD.

Randomised Therapy Sequences



Study Outcomes

This study will compare three primary therapeutic approaches in people with type-two diabetes. Predefined outcomes for each treatment sequence will include:

- overall mean reduction in fasting, prandial and HbA_{1c} glucose values
- proportion of subjects attaining glucose targets
- number and severity of hypoglycaemic episodes
- effects on weight, blood pressure, lipids and biochemical indices of cardiovascular risk
- side effects of medication and adverse events
- adherence with lifestyle, monitoring and therapies
- therapy satisfaction, health perception and quality of life

Study Coordination

This study is a general practice based academic study designed, run and analysed by the Diabetes Trials Unit at Oxford University with the central biochemistry laboratory at the Radcliffe Infirmary, Oxford. The principal investigator and study coordinator is Dr Nicolette Potts at the Diabetes Trials Unit.

For further information, please contact: Dr Nicolette Potts, Principal Investigator, GOOD Study Office, Diabetes Trials Unit, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK.
Tel: +44 (0) 1865 224124 Fax: +44 (0) 1865 224138 Email: good@dtu.ox.ac.uk

Appendix 2: Patient Information Leaflet

We would like to invite you to take part in an important new research study which is hoped will improve the care of people with type 2 diabetes. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives or GP before you make your decision. We would be pleased to provide any additional information should you wish. Thank you for your time.

What is the purpose of this study?

A large research study (UKPDS) published last year showed that the risk of complications in diabetic patients can be minimised by obtaining very good control of their blood sugar. The purpose of this new study is to find the best way to help people with diabetes in Oxfordshire achieve lower blood sugar levels and look after their health.

Why have I been chosen?

Your general practice has been selected from those in the Oxfordshire area who have agreed to take part in this study. The study will later be expanded to cover the whole of the UK.

Do I have to take part?

No, it is entirely your decision whether or not to take part. Should you wish to join the study you will be given this information sheet and would be asked to sign a consent form. You would be given a copy of both of these documents. If you decide to take part you would still be free to withdraw from the study at any time without giving a reason. This would in no way affect the standard of care that you receive from your practice team.

What would happen to me if I take part?

This study would provide more structured care than is usually available for people with type 2 diabetes in general practice. You would be invited to attend your practice at monthly intervals and would receive the latest information about diet and lifestyle issues from your practice team. Your blood sugar, blood pressure and blood fats would be monitored very carefully and your therapies adjusted to ensure your levels remained within the recommended ranges to reduce your risk of complications. In order to minimise the risk of complications and to achieve the best possible blood sugar control you might be advised to take more tablets than previously prescribed or possibly to use insulin therapy.

How would my treatment be decided?

In order to find out the best way to help people with diabetes achieve very good glucose control and stay healthy we need to know which of the treatments for diabetes work best. To do this we will use different treatments in different patients to see which ones are most effective. Computer systems are used to ensure that treatments are allocated randomly to different patients. We would advise you about the recommended ranges for your blood sugar, blood pressure and blood fats and would provide you with an individualised treatment plan at the start of the study detailing the sequence of treatments that would be used if your blood sugar became raised at any stage during the study.

What are the side effects of the treatments?

All the treatments that would be used in this study are recognised, safe treatments for diabetes. They include metformin, rosiglitazone, gliclazide, acarbose and repaglinide tablets, humalog and isophane insulins. We would ensure that all the agents are suitable for you before you join the study but as with all treatments side effects may occur. These include mild stomach upsets, rashes, headache and fatigue. Liver and kidney test abnormalities are rare but would be checked for regularly within this study. If you developed new symptoms or felt ill with any treatments you should be seen by your doctor and should notify Oxford research staff on tel 224124.

What would I have to do?

You would be asked to take your medication regularly and to visit your practice at monthly intervals. Blood tests for the study would be done mainly with your routine samples but you would be asked to record your blood sugar regularly at home imbetween visits. Information and equipment for this would be provided free of charge from your practice. We would also ask you to complete a questionnaire every few months to let us know how you feel about the care we had provided.

What are the possible benefits of taking part?

This study would provide the opportunity for you to obtain good control of your diabetes, reduce your risk of complications and help you to stay healthy for the future.

Your experiences in this study would also be of immense help in deciding which treatments would be best for diabetic people in the future. By helping you obtain excellent control of your blood sugar levels we hope to learn the best ways to help people with diabetes generally to improve their health.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatments that are being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

Once the research study nears completion your care will be continued by your general practice as usual. It is hoped that all the treatments being used will be widely available and could be continued by your general practice. If any treatments are not available or could not be prescribed we would ensure that similar agents are substituted in your standard care.

What if something goes wrong?

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Copies of these guidelines are available on request.

Will my participation in the study be kept confidential?

If you consent to take part in this study your medical records may be inspected by the company sponsoring the research for purposes of analysing the results, and by people from regulatory authorities who check that the study is being carried out correctly. Your name will not be disclosed outside your own general practice surgery, however.

What will happen to the results of the research study?

Publication of the results of the study are expected in 2003.

Who is organising and funding the research?

This study will be coordinated by the Diabetes Trials Unit at the Radcliffe Infirmary and will be funded by an NHS R&D and educational grant.

Who has reviewed the study?

The study has been approved by the Central Oxford Research and Ethics Committee.

How can I obtain further information about this study?

If you require any further information about this study please feel free to contact either your general practitioner or practice nurse. Additional information can also be obtained from Dr Nicolette Potts at the Diabetes Trials Unit (telephone : 01865 224124)

Thank you for taking the time to read this information

Appendix 3: Consent forms

CONSENT FORM –SCREENING

Subject Number: ☐-☐☐☐-☐☐☐ -☐

This form must be completed by the patient. Please initial the box after each question.

I confirm that I have read and understand the patient information sheet for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
I agree to take part in the study screening procedures.	☐

.....	.....
Name of Patient	Date
	.....
	Patient Signature
....	.....
Name of Practice Nurse	Date
	.....
	Nurse Signature

Appendix 4: Resource manual

VISIT 1: ELIGIBILITY VISIT (0 MONTHS)

VISIT 1

Completion of baseline food diary and quality of life questionnaires

Ask the patient to complete these forms in the waiting room prior to their appointment

Inform the patient about the study and the benefits of glucose control in reducing complications

Use the patient info leaflet, study introduction fact file and UKPDS information sheet

Resources available: UKPDS information sheet (A) Pt info and intro factfile

Issue a subject number to the patient

Issue the next number from the practice list. Document its use on the master list provided

Obtain signed written consent for eligibility checks

Complete the screening consent form and ask for the patient's signature.

Check quality of life questionnaire and food diary completion

Complete CRF pages 001 to 006 inclusive

Assess the patients eligibility to join the study using the eligibility fact file

Take baseline tests and urine measurements as listed on ARF

Provide lifestyle, dietary, exercise and smoking cessation leaflets

Issue DUK Diabetes for Beginners information and application forms if needed

Resources available: Fact file and leaflets on healthy living (B)

Arrange appointment for recruitment visit in 2 weeks time

Return CRF copies and samples to the Diabetes Trials Unit

Study Introduction (see UKPDS information sheet)

The UKPDS study showed us that the risk of complications in people with diabetes (heart disease, strokes, eye, kidney and foot problems) can be dramatically reduced by obtaining good glucose control. We now wish to help people with diabetes achieve these low blood glucose values, reduce their risk of complications and maintain their long term health.

We are looking for highly motivated individuals who would be interested in receiving more intensive diabetes care to reduce blood glucose levels and avoid these long term health problems.

Eligibility Assessment

Patients must be willing to attend monthly visits at their practice and possibly weekly visits for a short period if allocated to insulin.

These visits will usually last 30 minutes but some of them will be one hour. They will take place in the mornings and will involve a blood test and blood pressure check. It is important to check that this schedule is compatible with the patient's work commitments.

Patients must be willing to monitor their glucose values regularly at home.

14 home blood glucose values will be needed each week (7 on a weekday and 7 on a weekend day). A glucose meter and finger pricking devices will be provided for each study participant. Patients with poor visual acuity, mobility and dexterity or those who would be unable to monitor home glucose should be excluded.

Patients must be willing to have therapy doses changed when glucose values are high.

The study will aim to get both fasting and post meal glucose values as near normal as possible using a variety of different treatments. This is likely to require more treatments than the patient is currently taking. The patient should have social support at home in case of hypoglycaemia

Patients must be aware that insulin may be used if their glucose values remain high with tablets.

Insulin injections may be required. Education and equipment will be provided by practice and study staff but the patient should be aware of the implications on their job, insurance and driving and ensure these are compatible.

Patients must satisfy all exclusion and inclusion criteria for the study

These are listed on the eligibility and entry CRF in the subject folder

Fact file on the principles of healthy eating and diabetes.

Healthy Living and Diet

This section has been taken from the Food and Lifestyle Section in BALANCE for Beginners Type 2.British Diabetic Association pp36-47

The diet for a person with diabetes is not 'special', it is a healthy way of eating, recommended for everyone.

Six steps to eating a healthy diet

Eat regular meals based on starchy foods such as bread, pasta, chapatis, potatoes, rice and cereals. This will help you control your blood glucose levels. Wherever possible, choose high fibre varieties of these foods like wholemeal bread and wholemeal pasta.

Try to cut down on the fat you eat, particularly saturated fat as this type of fat is linked to heart disease. Eating less fat and fatty foods will also help you lose weight. Use less butter, margarine, cheese, and fatty meats, Choose low fat dairy foods like skimmed milk and low fat yogurt. Grill steam or oven bake rather than frying or cooking with oil or other fats.

Eat more fruit and vegetables aim for at least five portions a day to provide you with vitamins and fibre and balance your overall diet.

Cut down on sugar and sugary foods. This doesn't mean you need to try to eat a sugar-free diet. Use diet low sugar or sugar-free squashes and fizzy drinks. Sugary drinks cause blood glucose levels to rise quickly. Cut down on sugar, confectionery, cakes, sweets, and chocolates.

Use less salt, try flavoring foods with herbs and spices rather than adding salt.

Drink alcohol in moderation only. That's two units of alcohol a day for a woman and three units a day for a man. Remember never drink on an empty stomach as alcohol can increase the likelihood of hypoglycaemia (low blood glucose levels). And never drink and drive.

Advise about targets for personal weight control.

Avoid special diabetic products, e.g. sweets biscuits, jams

Resources available: Healthy eating leaflets (C)

Dietary and Exercise Advice

- Advise patient to control weight through diet and exercise
- Inform patients about benefits of exercise (weight control, increased insulin sensitivity, improved mobility, circulation and blood pressure, maintenance of bone density)
- Specify dietary changes required for individual
- Inform patients of recommended exercise requirements (30minutes/5 times a week)
- Consider how exercise can be integrated into patients daily routine eg walking stairs cf lifts
- Consider prescription exercise scheme

Resources available: Exercise information sheet (D)

Alcohol

- Advise about maximum alcohol intake 3U/day for men and 2U/day for women
- Outline DUK recommendations for alcohol consumption
- Advise that alcohol contains high calories and encourages weight gain
- Explain the risk of hypoglycaemia (with insulin and sulphonylureas) and delay with alcohol
- Advise avoidance of low sugar beers (high alcohol) and low alcohol beers (high sugar)
- Explain the dangers of drinking and driving

Resources available: Alcohol information sheet (E)

Smoking

Stopping smoking is one of the most positive things a person can do to improve their health. It is the single most important step that people with diabetes could take to reduce their risk of heart disease.

Nicotine is an addictive poison, which makes the heart, beat faster. This, in turn, makes blood pressure soar temporarily. It increases the risk of blood clots and adds to the damage that high blood pressure may cause to your heart. 43 different cancer causing substances have been identified in tobacco smoke

Giving up smoking decreases the risks dramatically.

Resources available: Smoking Leaflet E

VISIT 2: RECRUITMENT VISIT (0.5 MONTHS)

VISIT 2

Recheck eligibility for study entry (CRF 007)

Check blood test results from previous visit.

Answer any questions that the patient may have about the study.

If the patient is ineligible or decides not to enter the study complete Q11 CRF007

Obtain full signed written consent for study entrants (*GP)

Assign subject folder for each study entrant

Dietary review using patient food diary entries

Resources available: Dietary information sheet and fact file (F)

Blood glucose monitoring training

Observe current technique or teach patients how to monitor home glucose

Issue equipment and diary. Discuss timing of tests

Resources available: Glucose monitoring information sheet and fact file (G)

Cardiovascular review (*GP)

Using risk data from the study centre consider aspirin, blood pressure and lipid therapies

Resources available: Cardiovascular information sheets and fact file (H) and leaflets

Issue study card, glucose diary, meter and educational leaflets

Arrange fasting appointment for 2 weeks time

Ask the patient to fast from midnight the night before their next appointment

Remind the patient to bring their glucose diary and meter to download results at the next visit.

Thank the patient for their participation

Return copies of CRF and consent forms and samples to DTU

Fact file for blood glucose monitoring

Why monitor

Home glucose monitoring results are central to this study and will be used to adjust doses of both oral and insulin therapies. They will provide information to enable diabetes management to be tailored to the individual's lifestyle and to be adjusted during illness and stress.

When to monitor

The patient will be asked to take to take two 7 point profiles a week. Ideally we need one profile on a weekday and one on the weekend.

Requested plan for the week

Blood Test Results

Days of the week	Before Breakfast	2 Hrs After Breakfast	Before Mid-Day Mea	2 Hrs After Mid-Day Meal	Before Evening Meal	2 Hrs After Evening Meal	Before Bed
Mon							
Tues							
Wed	X	X	X	X	X	X	X
Thurs							
Fri							
Sat							
Sun	X	X	X	X	X	X	X

7 point profiles provide a more accurate picture of the patient's blood glucose control than isolated blood glucose readings on different days. The latter are harder to assess without knowing the morning fasting value as this reading affects the results for the whole day. Patients should be encouraged to jot down any information about meals out or illnesses in the comments section of their diary. Extra readings should be taken if the patient feels odd or unwell; this is one way of obtaining hypoglycaemia warning and will enable the patient to take the appropriate action. (see sections on hypoglycaemia and sick day rules).

How to Monitor

The test area needs to be well covered in blood and this can be a problem for some patients. The skin must be cleaned using soap and water, before the finger is pricked to avoid accidental contamination from substances on the skin. Spirit swabs should not be used to clean the skin as the spirit may affect results.To help improve blood flow the patient my wash his or her hands in warm water and swing the arm vigorously for one minute. The best fingers to use are the third and fourth fingers as the skin is often softer and less thick. The pulp at the top of the finger is sometimes used but this may be painful and bruising can occur. The side of the end of the finger away from the thumb is the preferred site for lancing (less painful). When the skin has been pierced, the drop of blood should be allowed to hang on the end of the finger, as the test strip requires that only blood is

placed on the strip. The blood should not be spread over the pad using the finger. Squeezing the finger at the top will suppress blood flow. Milking the finger from the base will elicit a good sized drop.

Disposal of used equipment for patients

Lancets should be made safe before disposal. Most of them have a plastic bobble that is removed prior to lancing; used lancets should be pushed into the side of the bobble. (If the needle is reinserted into its original hole the bobble may fall off) after the lancet has been covered it should be placed into a strong plastic container like an old shampoo bottle with a screw top lid or an empty soft drinks can. Once the container is full it should be sealed securely, wrapped up and disposed of in dustbin. Blood stained cotton wool, tissues and strips etc should be disposed of immediately in the household rubbish.

Blood Sugar Goals

Time	Target range (mmol)	Additional treatment if (mmol)
Before breakfast	4 - 6	More than 6
2 hours after breakfast	4 - 8	More than 8
Before lunch	4 - 6	More than 6
2 hours after lunch	4 - 8	More than 8
Before dinner	4 - 6	More than 6
2 hours after dinner	4 – 8	More than 8
Before bed	4 – 6	More than 6

HbA_{1c} Measurements

Glycosylated or glycated haemoglobin measurement is used to assess blood glucose control over the previous six to eight weeks. HbA_{1c} measurements will be taken at monthly intervals throughout the feasibility study and used as a check against the home blood glucose readings used to adjust therapies. The normal range for HbA_{1c} at the central biochemistry laboratory for this study is 4.7% - 6.4%.

Cardiovascular Risk Fact File

CVS Risk

Facts about Coronary heart disease (CHD).[1]

Coronary heart disease is much more common among people with diabetes and is the main cause of death (up to 50% in type 2 diabetes). This increased risk applies even to those with marginally elevated blood glucose levels (greater than 6 mmol/l). The risk of a heart attack (MI) is increased in type 2 diabetes by two to three times and risk factors are cumulative.

Normal Ranges for Cardiovascular Risk Factors

Cardiovascular risk factor	Good	Borderline	Poor
Total cholesterol (mmol/l)	<5.2	5.2-6.5	>6.5
HDL-cholesterol (mmol/l)	>1.1	0.9-1.1	<0.9
Triglycerides (mmol/l)	<1.7	1.7-2.2	>2.2
Fasting glucose	4.4-6.1	6.2-7.8	>7.8
Post prandial glucose	4.4-8.0	8.1-10.0	>10.0
HbA_{1c} (%)	<6.2	6.2-7.5	>7.5
Blood pressure (mmHg)	<135/80	Between	>160/95
Smoking status	None	----	Current
BMI Males (kg/m^2)	20-25	26-27	>27
BMI Females (kg/m^2)	19-24	25-26	>26

Hypertension

Blood pressure will be measured at every visit. If blood pressure exceeds target values (more than 135mmHg systolic or more than 80mmHg diastolic) on any occasion lifestyle advice should be offered. Patients should be encouraged to stop smoking, achieve their ideal body weight, limit alcohol intake to within recommended guidelines, eat a sensible low fat, low salt, high fibre diet, avoid persistent stress and take regular exercise (20 minutes five times a week).

If BP levels remain elevated on two or more consecutive visits an ACE inhibitor should be prescribed. Blood pressure should be monitored monthly and doses of this agent increased accordingly. If maximal therapy is reached a second agent (alpha-blocker or calcium antagonist) should be added. These drug additions should be supervised by the patient's GP.

High Lipid Levels

A full lipid profile will be checked on the initial study visit. If lipid values are raised above target levels (see table above) lifestyle changes will initially be instituted. A high fibre, low fat diet should be recommended, alcohol intake limited, physical activity increased and ideal body weight sought. Elevated lipid levels at this first study visit should be rechecked at six months. Drug treatment with statins or fibrates should be commenced for persistently elevated values.

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[1] Fox C and MacKinnon M 1999 Vital Diabetes. Your essential reference for diabetes management in primary care. Class Health. London.

The patient's coronary risk will be assessed at the DTU using a coronary risk prediction chart[2] and recommendations for cardiovascular risk management will be returned. This should be reviewed by the patient's GP.

Smoking

The patient's smoking status should be assessed at the beginning of the study. Smokers should be provided with encouragement and support to stop smoking. Nicotine replacement therapy should be considered and follow up support provided for patients who stop smoking.

Obesity

Weight is measured at each visit and those patients who exceed body mass index targets should receive additional advice on weight loss, diet and exercise.

Cardiovascular risk Guidelines

The study centre is encouraging cardiovascular risk management according to standardised national guidelines which are enclosed.

Each patient's cardiovascular risk will be assessed at the study centre using a coronary risk prediction chart[3]. Using this individualised assessment on CRF 008, and following the guidelines supplied and encouraged by the study, consider aspirin, blood pressure and lipid therapies as appropriate. Please complete the "action taken" column on CRF 008.

The study will monitor lipids annually. Practices are advised to follow guidelines with more frequent monitoring as recommended.

Hypertension Guidelines

Resources available: WHO–ISH Blood Pressure Guidelines. Q

Cardiovascular Risk Guidelines

Resources available: Cardiovascular Risk Guidelines. Q

[2] Wood D et al. Joint British Recommendations on Prevention of Coronary Heart Disease in Clinical Practice. Heart. Suppl. 2 Dec 1998 Vol 80

[3] Wood D et al. Joint British recommendations on prevention of coronary heart disease in clinical practice. HEART Supplement 2 December 1998 Vol. 80

Cardiovascular Risk Factors: Explanations for Patients

Hypertension

Blood pressure is the force with which your heart pumps blood round your body.

Hypertension is the medical term for high blood pressure and raised blood pressure is very common in type 2 diabetes (40-50%). Aggressive treatment reduces vascular complications in diabetics and as a result the BP targets and threshold for starting treatment are lower than the general population. The target blood pressure in people with diabetes is less than 135 mmHg systolic and less than 80mmHg diastolic. Older people should be treated as enthusiastically as younger people as they are more likely to derive early benefits.

High blood pressure does not usually cause any symptoms but if severe can occasionally produce headaches, dizziness or visual disturbance.

There is no cure but it can be treated easily and effectively. Lifestyle changes should initially be made and drugs commenced if blood pressure remains high. ACE inhibitor agents are particularly beneficial in diabetic people as they have a protective effect on kidneys and possibly eyes, and reduce mortality over and above their effect on blood pressure.

Often two or more drugs are required to achieve the target BP of 135/80mmHg.

All drugs used for treating hypertension have well-recognised side effects.

-Thiazides; low serum K+, raised blood glucose and impotence:
-Beta blockers: may worsen asthma and peripheral vascular disease
-ACE inhibitors; cough, worsening of renal function, oedema
-Calcium blocker: flushing, headache, and oedema.

Smoking

The general risks of smoking need to be discussed and the additional risk of smoking and diabetes stressed. Encouragement and support should be provided to help patient stop smoking.

Resources available: Smoking information sheets (I)

Obesity

The general risk of obesity needs to be discussed and the additional risk of obesity and diabetes need to be stressed.

Resources available: Weight reduction information (J) sheets

VISIT 3: RANDOMISATION VISIT (1 MONTH)

VISIT 3

Issue and check completion of quality of life questionnaires

Ask the patient to complete forms in the waiting room prior to their appointment

Check their completion at the beginning of their visit.

Complete CRF 009 – 011 and 021 if any adverse events have occurred

Resources available: Adherence fact file

Discuss blood glucose monitoring results and diary completion

Troubleshoot any problems that have been experienced so far. Download the meter results

Perform a fasting clinic capillary glucose sample and take fasting blood tests

Discuss randomised medication and issue treatment plan (H GP)

Inform the patient of their expected treatment sequence in the study

Provide info about action, duration and side effects of drugs

Resources available: Drug fact file and Patient Treatment Plans J

Issue study treatment unless the majority of FPG values with gating approach are below 6mmol

Ensure patient has prescription exemption certificate

Advise patient to contact DVLA and their car insurance company re commencing tablets

Resources available: DVLA information sheet K

Discuss hypoglycaemia management (emphasise in glipizide group)

Resources available: Hypoglycaemia factfile and information sheet (L)

Arrange fasting appointment for one months time

Ask patient to bring their blood glucose diary and meter at this visit.

Return data copies, consent copy and samples to DTU.

Drug Information for Practice Nurses

Drug Fact File

Metformin

Metformin is a member of the biguanide group of drugs. It works by improving the body's ability to use insulin more efficiently. When cells become more sensitive to insulin, the body doesn't require as much insulin to keep blood glucose controlled. This reduces the workload of an already- overworked pancreas. Metformin also blocks the liver from producing new glucose (glucose production by the liver is the main reason for high glucose levels in the morning) and delays the carbohydrate absorption from the gut.

Common side effects of metformin include nausea, diarrhoea and abdominal bloating. These symptoms are usually transient and lessen within a few weeks. Very rarely lactic acidosis or decreased vitamin B12 absorption may occur.

Metformin may be known under the brand name of glucophage. The 850mg strength tablet will be used in this study. This tablet should be commenced once a day, with or after food, at one month (treatment plans A and B). A twice daily dose will be used at two months and a three times a day dose used at four months.

Glipizide

Glipizide is a member of a group of drugs called sulphonylureas, which are particularly useful for lowering blood sugar. Glipizide works by stimulating the beta cells in the pancreas to make more insulin.

The commonest side effect of glipizide is weight gain. Glipizide can also produce hypoglyaemia by lowering blood glucose values too much. Other side effects are generally mild and infrequent, and include gastrointestinal disturbance, headaches, dizziness, drowsiness and transient rashes. These symptoms usually only occur within the first 6 to 8 weeks of treatment. Very rarely blood changes including anaemia and low platelet count may occur.

Glipizide may also be known under the brand names of minodiab or glibenese. It is dispensed as a 5mg tablet and should be commenced on a once daily basis at one month into the study (treatment plans E and F). Patients should take this tablet before their breakfast. A twice daily dose may be required at two and four months and this should be taken before breakfast and before the main meal.

Rosiglitazone

Rosiglitazone is a new anti-diabetic agent and is a member of the thiazolidinedione group of drugs. It is widely used in the USA but the UK license and launch is not expected until later this year. Rosiglitazone is therefore being used under a special trial license in this study. Rosiglitazone works by improving the body's sensitivity to insulin, enabling more efficient insulin use and lower blood glucose levels.

Side effects include weight gain and pedal oedema in number of patients. Previous thiazolidinedione drugs have increased liver enzymes and caused liver problems. Rosiglitazone does not produce liver toxicity careful monitoring of liver enzymes will be performed throughout this study.

Patients will be commenced on a 2mg tablet at one month (treatment plans C and D) and this will be force titrated to 2mg twice daily at two months and 4mg twice daily at four months irrespective of the gating approach as a result of the delayed effect of this agent on blood glucose.

Humalog Insulin (Lispro)

Humalog insulin is a rapid acting insulin which reduces blood glucose levels much more quickly than regular (soluble) insulin. The peak action of humalog is one hour after subcutaneous injection and the duration of action is approximately four hours (also less than regular insulin). Humalog is therefore very useful for controlling post meal blood glucose values. Its short action means that hypos are reduced and there is increased warning of hypoglycaemia in those that have reduced awareness. Humalog has also been associated with an overall reduction of nocturnal hypoglycaemia (12%)

Humalog, because of its rapid action, should be taken just when the patient is about to eat, although research suggests that it can also be taken just after a meal and achieve the same result.

Taken from Clinical Experience of a Rapid Acting Insulin Analogue (insulin Lispro)
Report on a European round Table Meeting Practical Diabetes International Supplement June/July 1997 Vol.14 No.4

Repaglinide

Repaglinide is a short acting sulphonylurea which works by stimulating insulin release from the pancreatic beta cells. It is particularly useful for controlling the sharp increase in blood sugar after a meal (postprandial glucose).

Side effects include nausea, diarrhoea, constipation, abdominal pain, rashes and very rarely elevated liver enzymes.

A 500 microgram strength repaglinide tablet will be used initially in this study. This should be taken within thirty minutes of each meal. The dose will be increased to a 2mg strength tablet with meals at four months and two 2mg tablets with meals at five months. The maximum daily dose should not exceed 16mg. Repaglinide should be omitted if meals are missed.

Acarbose

Acarbose is a member of the alplia glucosidase inhibitors. It blocks the action of enzymes in the gut and prevents complex sugars being converted to simple sugars. Absorption of glucose is delayed and residual sugars are broken down in the large bowel to cause gas. Side effects include abdominal distension, flatulence and diarrhoea, all of which are made worst by a high sugar diet. A 50mg tablet of acarbose should be commenced initially with the largest meal. Twice daily and possibly three times daily doses will be used at three and four months.

Fact File on Hypoglycaemia

Hypoglycaemia

Adapted from J Farr and M Watkinson *1993 2nd edition Diabetes A Guide to Patient Management for Practice Nurses* Radcliffe Medical Press. pp68-69.

It is essential that patients particularly those on glipizide therapy understand the causes, signs and symptoms of hypoglycaemia. Relatives should also know what to do in the event of hypoglycaemia. Often someone close to the patient recognises an episode before the patient by noting a glazed look in the eye or a change in personality.

Hypoglycaemia may be caused by taking too much insulin or glipizide, delaying meals, eating too little carbohydrate, drinking excess alcohol or taking excess exercise.

Signs and symptoms

The symptoms are caused by a lack of blood glucose to the brain and the release of adrenaline in response to this low glucose. People with diabetes vary in the extent to which they get warning of hypoglycaemia. Older patients especially those with autonomic neuropathy may experience few symptoms or be unaware of hypoglycaemia.

The symptoms may include:

1. Weakness
2. Lethargy, drowsiness or inability to wake up
3. Tremor
4. Paraesthesia or tingling round mouth and in finger tips
5. Double vision
6. Lack of concentration
7. Hunger
8. Headache
9. Rapid pulse or pounding heart

The signs may include:

1. Pallor
2. Excessive sweating
3. Aggressive, unusual behaviour or irritability
4. Slurred speech

Hypoglycaemia symptoms vary between people but are usually the same for a given person. Patients should be encouraged to check their blood glucose every time they feel strange so that they can recognise their own reactions to low glucose levels. If a hypo occurs at night the patient may experience frequent nightmares and have early morning headaches the next day.

When blood glucose drops below normal levels, adrenaline, glucagon and corticosteroids are released. Gluconeogenesis causes glucose produced by the liver to be released into the bloodstream and glycogenolysis causes conversion of liver glycogen to glucose.This is also released into the bloodstream. This tends to correct the low sugar level and may even rebound causing high glucose levels. For this reason it is important not to 'over treat' a hypoglycaemic patient, even though they may be feeling extremely hungry.

Classification and Management of Hypoglycaemia

These classifications will be needed for CRF 009

Grade 1 - Mild hypoglycaemia (can be dealt with by the patient)

Mild symptoms and glucose levels of 2-3mmol/l. The patient may feel 'odd' or 'funny' but are able to remedy the situation quickly. Advise the patient to check their blood glucose value. If the glucose value is normal (>4mmol) then the episode is unlikely to be due to hypoglycaemia.

Patients on glipizide or inulin therapy should carry emergency fast acting carbohydrate with them. For mild symptoms with glucose levels of 2-3 mmol/l patients should be advised to take 10 grams of carbohydrate (3 glucose tablets or 2 tablespoonfuls of Lucozade or 2 tea spoonfuls of sugar in a drink).If symptoms persist after 10 minutes a further 10 grams of carbohydrate should be taken. If glucose levels are less than 2,5 mmol/l and a meal is not due to be eaten they should take 20 grams of carbohydrate. It is important to follow any of these short-acting carbohydrates with a longer-acting, high fibre snack (a sandwich or a biscuit) or the next meal if it is due.

Grade 2 - Mild to moderate hypoglycaemia (can be dealt with by the patient)

The patient has more severe symptoms and glucose values less than 2.5 mmol/l. The symptoms are more severe than in mild hypoglycaemia but the patient is still able to deal with the episode on their own.Treatment is as above but if a meal is not due to be eaten they should take 20 grams of carbohydrate or double the amounts above.

Grade 3 - Moderate hypoglycaemia (requires help from another person)

If hypoglycaemia is more severe the patients may be confused and unable to help themselves. In this situation they require help from others to manage their hypo.

Friends/family need to be taught that unusual behaviour such as rudeness, aggression or appearing to be drunk may be signs of hypoglycaemia. At this stage it is easier and quicker to give the patient sugar in liquid form or use Hypostop. Examples of sugar in liquid form are a small glass of cola (not diet) or lucozade or ribena or a tablespoon of sugar dissolved in water. Hypostop is a dextrose gel, which is available on prescription and can be prescribed for the patient if you think it advisable it can also be bought over the counter. It can be used to squirt glucose into the mouth (the inside of the cheeks) and is rapidly absorbed from the lining of the mouth. It is not meant to be swallowed. As it tastes very sweet it may be unpleasant for the patient and they may spit it out. Treacle jam or honey can also be used if this is a problem.

Grade 4 - Severe hypoglycaemia (requires medical help)

Severe hypoglycaemia involving loss of consciousness requires medical help. The patient should be placed in the recovery position and medical help summoned. Glucagon should be injected if available. This hormone releases glucose from the liver and is a quick, effective way to reverse severe hypos. The patient will usually regain consciousness within 5 to 10 minutes. Once conscious the patient should take carbohydrates by mouth. Glucagon injections are available on prescription. If the patient is unconscious and glucagon is not available an ambulance should be summoned.

VISIT 4: DOSE REVIEW (MONTH 2)

VISIT 4

Issue and check completion of quality of life questionnaires

Ask the patient to complete these forms in the waiting room

Check their completion at the beginning of their visit.

Complete CRF 009 – 012 plus 021 if any adverse events have occurred

Discuss blood glucose monitoring results and diary completion

Troubleshoot any problems that have been experienced so far and download the meter results

Perform a clinic capillary glucose sample and take fasting blood tests

Ask the patient to take the capillary sample and check their technique

Ensure the patient has fasted before taking their blood tests

Review adherence with study treatment

Resources Available: Adherence fact file

Increase tablet doses unless the majority of FPG values are below 6mmol with gating approach

Resources Available: Medication Adjustment fact file

Discuss hypoglycaemia and its management

Arrange a fasting appointment for one months time

Ask the patient to bring their blood glucose diary and meter with them.

Return the copies of all forms and samples to the DTU

Adherence

Adherence Factfile

Adherence is defined as the extent to which a person's behaviour coincides with health advice.[4]

Adherence to Lifestyle Advice

Lifestyle changes are difficult to make and once made are often hard to sustain.
CRF 011 is attempting to chart any changes that the patient does make in their diet following the initial lifestyle advice given at the first visit. If you feel the patient would benefit from recapping on dietary guidelines or losing weight (patient handout H) then do.

Adherence with medication (tablets or insulin)

Measurement of adherence is difficult and for the purposes of this study we shall simply be asking the patient how well they took their treatments and assessing their returned medication or drug boxes.

Patients who agree to take part in this study have already demonstrated motivation towards intensive treatment. Their experience with different treatment sequences is invaluable for the establishment of treatment policies in the future.

Adherence with therapy should be explored and reasons for problems documented.

The following areas should be discussed in non-concordant patients:

1. Forgetfulness. Various strategies can be used to jog the memory; leaving tablets or reminder notes in obvious places, setting an alarm, asking a relative to provide a reminder or using dosset boxes.
2. Side effects. Patient should be encouraged to inform us about any side effects they experience. If severe, the study centre should be informed. Correct administration of therapy should be checked.
3. Misunderstanding. The patient may have misunderstood the instructions for taking their tablets.
4. Fear of hypos. A review of the patients knowledge of hypos and their management together with a review of the action and duration of their medication might be needed.
5. Loss of medication or equipment. This should be reported to the study centre. Extra medication or equipment should be supplied.

Adherence with home blood glucose monitoring

This is a vital component of this study as patient home glucose monitoring values are used to make therapy changes. Meter readings are downloaded at each visit and will be compared to the summary obtained from the patients blood glucose diary. Research[5] shows that if patients realise their meter readings will be downloaded more accurate reporting of behaviour results.

Possible reasons for non-adherence with blood glucose monitoring should be discussed.

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[4] McNabb W L Adherence in Diabetes: Can We Define It? And Can We Measure It? Diabetes Care, volume 20, number 2, February 1997

[5] Mazze et al. Psychological and Social Correlates of Glycemic Control. Diabetes Care 7:360-366, 1984 cited in McNabb W L Adherence in Diabetes: Can We Define It? And Can We Measure It? Diabetes Care, volume 20, number 2, February 1997

- Pain. Ensure the patient's technique is good. Every visit you will have an opportunity to observe the patient performing a test. Ensure the patient adjusts the finger-pricking device to a suitable depth uses a new lancet each time. These can blunt with repeated use and cause pain. Ensure the patient is using a good site to take the blood. If they are using computer keyboards regularly or playing the guitar, then advise them on which sites to avoid. See the glucose monitoring factfile.
- Inconvenience. Blood glucose monitoring is inconvenient and encouragement may be required. If daytime readings are difficult during work hours then all readings should be taken at the weekend.
- Forgetfulness. Various strategies can be used to jog the memory. Leaving reminder notes in an obvious place or setting an alarm two hours after meals for prandial measurements. The study will provide each patient with a small stopwatch to help with this timing and the importance of these readings should be stressed
- Misunderstanding. The patient may not have understood the instructions for monitoring. Check that they can repeat them back to you and can make plans about when to take the reading when their routine is disrupted, e.g. late meal, evening out or journeying overnight.
- Equipment loss. If the patient has lost the meter or finger-pricking device they should let the practice know immediately. The study will supply the practice with extra meters for such an event.
- Frustration. Patients may interpret high and low blood glucose results as failure and feel frustrated, guilty, or demoralised thus testing less frequently. Please provide reassurance. Regular monitoring of diabetes enables treatment to be initiated as necessary to reduce blood glucose levels and delay the effects of diabetes.

An assessment of attitudes towards illness and medication may also be required. Suggested open questions for this assessment include:

- Identify patients past behaviour in terms of compliance and tablet taking
- Establish patients attitudes towards diabetes and its treatment
- What is the thing that worries you most about your diabetes
- Do you value taking these tablets? Why or why not?
- Establish patients perceived behavioural control / illness beliefs
- Who is primarily responsible for your diabetes?
- How important are the views of others to you taking your tablets
- Discuss patients intentions to take medication
- Do you intend to take these tablets?
- How willing would you be to take more treatment for your diabetes?
- Educational approach tailored to patients worries and attitudes
- Evaluation of tablet effects
- Do you get any of the following side effects from your tablets?
- Do these side effects matter to you?
- How much X could you tolerate to prevent Y?

VISIT 5: ADDITION OF PRANDIAL AGENT (MONTH 3)

VISIT 5

Issue and check completion of quality of life questionnaires

Ask patient to complete these forms in the waiting room prior to their appointment

Check their completion at the beginning of their visit.

Complete CRF 009 – 012 and 021 if adverse events have occurred

Discuss blood glucose monitoring results and diary completion

Troubleshoot any problems that have been experienced so far. Download the meter results.

Perform a clinic capillary glucose sample and take fasting blood tests

Ask the patient to take the capillary sample and check their technique

Ensure the patient has fasted before taking their blood tests

Review adherence with study treatment

Use the adherence fact file.

Adjust dose of basal agent using gating approach.

Add prandial agent unless majority of home glucose values are PPG <8mmol (H GP)

Resources Available: Medication Adjustment fact file

Patients commencing insulin: Arrange weekly appointments for 3 weeks to teach insulin skills and education topics: injections, insulin storage, needle disposal, BG testing, hypos, sick days, driving, emergencies, contact numbers. Prescribe Hypostop, BD safe clip and pen needles.

Patients commencing repaglinide: give drug information

Resources available: Insulin factfile and checklist

Discuss hypoglycaemia and its management

Arrange a fasting appointment for one months time

Ask the patient to fast from midnight and bring their blood glucose diary and meter with them.

Return the copies of all forms and samples to the DTU

Guide to adjusting medication using home glucose values

Medication Adjustment

Check each profile for any out of range values, values which seem higher or lower than normal. Ask the patient if they can recall the day in question. Did they have a cold, flu or a stomach upset, illness of any sort? Had they been out celebrating the night before and eaten or drank alcohol to excess? Did they have a hypo episode the day before? Please document in the patient's diary the any clues given by the patient. Encourage the patient to jot down any information about meals out or illnesses in the comments section of their blood glucose diary.

Each month you will need to assess the last two weeks of home blood glucose values: 16 fasting and 12 prandial measurements should be present.

Use the gating approach on the CRF to calculate the number of readings above, below and in the target range for fasting and prandial glucose.

If the majority of the pre-meal readings (at least 75% or 3 out of every 4) are 6.0mmol or below then medication should remain at the current dose. If more then 25% of these values or 1 in every 4 readings are higher than 6.0 then the patient should be prescribed an increased dose of the basal therapy as outlined in their treatment plan.

If the majority of the post-meal readings (at least 75% or 3 out of every 4) are 8.0mmol or below then medication should remain at the current dose. If more then 25% of these values or 1 in every 4 readings are higher than 8.0 then the patient should be prescribed an increased dose of the prandial therapy as outlined in their treatment plan.

Consult the study staff for all queries relating to adjustment of study medication.

Insulin Fact File

Patients commenced on humalog or isophane insulin should receive information about the following aspects of their treatment.

Injection technique	Correct use of pen device (see teaching plan)
Injection sites	Availability and rotation of sites. Diagram and patient handout M
Storage of insulin	Bottle/cartridge in use at room temperature. Spares in refrigerator
Disposal of sharps	In sealed plastic bottle/can using BD safeclip for needles
Insulin doses	Starting dose and adjustment in clinic based on BG values
Insulin action	Action and duration of humalog and isophane insulin
Special situations	Hypoglycaemia, hyperglycaemia and DVLA handouts N,O and P.

The recommended way to inject is to pinch up the skin and inject at an angle of 90 degrees this will deliver the insulin subcutaneously. If the injection is given at less of an angle then it will be absorbed too rapidly within the epidermis of the skin which has more blood vessels than the subcutaneous fat. The site should be relaxed, advise on the need for quick needle insertion to enable a more comfortable injection.

Injection sites

Insulin should be injected into an area of the body where there is sufficient subcutaneous fat and an absence of large superficial veins. There are different absorption rates from different areas of the body. The smile line under the belly button has the fastest absorption rate, next is the arms then the thighs and buttocks. To avoid fluctuating absorption rates and for better glycaemic control it is important that one area is used at the same time each day eg the abdomen before breakfast, the thigh before lunch and possibly the arm before the evening meal. Patients must be taught not to target the same site. Repeatedly injecting insulin into the same site causes the formation of large pads of hard lumpy subcutaneous fat (lipohypertrophy) from which the absorption rate of insulin is erratic. These areas are also unsightly and cause distress. Encourage patients not to inject into the same square inch for at lest a week. Things that affect absorption include taking a hot bath immediately after injection or strenuous exercise following an injection into the thigh or even sitting in the sun on a hot summer's day following an injection. Increased peripheral perfusion to the injection area will increase the absorption rate of the insulin from that area.

Storage of insulin

Insulin vials/cartridges do not need to be kept in the fridge if they are in current use, but they should be kept out of direct sunlight and away from heat

Disposal of cartridges and needles

All sharps should be recapped carefully and disposed of into a sharps bin or into a strong plastic container like an old shampoo bottle with a screw top lid. Once the container is full it should be sealed securely, wrapped up and disposed of in a bin.

Care of equipment

Patients can use their disposable insulin syringes and pen needles for up to five injections, although some people may find that the needle becomes blunt before then, each patient will need to figure out the number of times it remains comfortable to use the disposable insulin syringes or pen needles. After use, disposable insulin syringes should be "pumped" a few times to get rid of any insulin left in the needle and re-capped. Syringes should be thrown away if the dose markings can't be read or the needle is bent or has been contaminated.

Adjustment of isophane insulin doses

Use the slide rule as practiced on the training day to determine the starting dose of isophane insulin for each patient and verify with study staff. Doses should then be adjusted initially at weekly intervals for one month. Increasing the bedtime isophane dose will reduce morning fasting glucose values. If evening fasting glucose values are greater than 6mmol a morning isophane injection should be commenced. Rough guidelines for dose adjustments are provided below but the optimum quantity of insulin depends on the individual, their lifestyle and BMI.

Majority of FPG values	Isophane dose change
Below 4.0 mmol	Reduce isophane by 1 – 2 units
4.1 – 6.0 mmol	Continue isophane dose
6.1 –8.0 mmol	Increase isophane by 1 –2 unit
8.1 – 10.0 mmol	Increase isophane by 2 units
Above 10.0 mmol	Increase isophane by 2 - 4 units

Adjustment of humalog insulin doses

2 units of humalog insulin should be commenced with each meal. Doses should be adjusted initially at weekly intervals. If the majority of post meal glucose values for a particular meal are high the humalog dose with that meal should be raised. Rough guidelines are shown below but obviously ideal dose adjustments will depend on the individual and their BMI. Increased doses may be needed if patients have a BMI above 30.

Majority of PPG values for this meal	Humalog dose change for this meal
Below 4.0mmol	Reduce humalog by 1 – 2 units
4.1 – 8.0 mmol	Continue humalog dose
8.1 –10.0 mmol	Increase humalog by 1 –2 unit
10.1 – 12.0 mmol	Increase humalog by 2 units
Above 12.0 mmol	Increase humalog by 2 - 4 units

The effect of this dose change on PPG values should be monitored and reviewed weekly aiming for the target range of 4-8mmol. Telephone contact from the study centre is available where dose adjustments are problematical.

Prevention of Hypoglycaemia for people on insulin therapy

Understanding Hypoglycaemia

Adapted from Diabetes Education Study Group of the European Association for the Study of Diabetes. Survival Kit: The five-minute Education Kit. *Diabetic Medicine,* 1995;12:1022-1043

Start with open questions to identify the patient's knowledge of hypoglycaemia and to assess the educational reinforcements necessary. Some suggested opening questions are as follows:

1. **Have you ever experienced an episode of hypoglycaemia?**

2. **What do you know about the effect of insulin on you?**

   Discuss the normal range of blood glucose, the changes in the level of blood glucose as a result of meals and exercise and the effect of insulin on blood glucose.

3. **Do you know what happens to you when your blood sugar is too low, a situation we refer to as hypoglycaemia? Do you know anybody who takes insulin and how they feel when they have hypoglycaemia?**

   Discuss the symptoms and signs of hypoglycaemia. If the patient is aware of hypoglycaemic coma you should stress its good prognosis and reassure them.

4. **What events or situations might result in low blood sugar?**

   Discuss the effect of insulin on blood glucose and relate it to the regimen prescribed with emphasis on the dose and time of insulin administration. Explain how meals or snacks, alcohol and exercise affect blood glucose and mention the possibility of hypoglycaemia several hours after exercise or even the following day

5. **How do you think you can prevent hypoglycaemia?**

   Stress the need not to omit or delay meals and advise ingestion of extra carbohydrate before exercise. Stress the need to check blood glucose readings whenever they feel the symptoms of hypoglycaemia so that they can begin to recognise their individual reactions to low blood sugar levels.

Objectives:

For the patient to understand what hypoglycaemia is, how it occurs, how to prevent it, how it feels, how to recognise it and what action to take to treat it.

Resources available: DUK Hypoglycaemia information sheet (M)

Hyperglycaemia Fact File

Adapted from J Farr and M Watkinson *1993 second edition Diabetes A Guide to Patient Management for Practice Nurses* Radcliffe Medical Press. p67-68

Hyperglycaemia is defined as a glucose level of >12 mmol/l. It can result from non-compliance with treatment, untreated diabetes, too much food, the wrong type of food, infections/ illness, insufficient medication or insulin, overusing particular injection sites, poor injection technique, reduction of physical activity, concurrent medication affecting glucose control (eg steroid treatment), stress or life changes (eg retirement, bereavement) or weight increase.

Fever and sick days

During illness, particularly infections, glucose levels may rise considerably. When the body is stressed it produces larger amounts of the stress hormones (adrenaline and cortisol). These hormones raise glucose levels by stimulating glycogenolysis and gluconeogenesis.

The following principles will enable diabetic people to cope safely with illness.

- Insulin and tablets must never be stopped even if the patient is not eating. The body releases stored glucose and produces some glucose in the fasting state. This is increased during episodes of illness or stress.

- Test blood glucose levels at least every six hours. Ensure a friend/relative also knows how to test the patient's blood. These regular tests are necessary to provide information for tablet and insulin dose adjustments.

- If blood glucose levels are rising the amount of tablets or insulin may need to be increased. If a patient is on the maximum dosage of tablets they may need to have insulin injections for the duration of the illness.

- The patient should be encouraged to drink at least 2 - 3 litres of non-sugary fluids every day, in order to prevent dehydration, which may be a result of hyperglycaemia (sugary fluids exacerbate the high blood glucose levels).

- If blood sugar levels are very high, urine tests for ketones should be performed

Medical help must be sought when;

- vomiting and / or diarrhoea persists for more than 24 hours
- the patient is unable to tolerate oral fluids
- the patient cannot prevent their glucose levels rising despite increasing their tablets or insulin doses
- the patient develops diabetic ketoacidosis

Hospitalisation is likely to occur in cases of:

- persistence of vomiting/diarrhoea despite antiemetic or antidiarrhoea treatment
- diabetic ketoacidosis
- dehydration that requires intravenous fluid therapy
- infection that required intravenous antibiotic therapy
- hyperosmolar non-ketotic diabetic coma

Teaching Plan for Humapen

Objectives: For the patient to be able to;

1. Identify the different parts of the equipment required.
2. Break down, load and assemble the Humapen Insulin delivery device.
3. Prime the pen and dial up the correct dose.
4. Identify suitable injection sites.
5. Know the importance of rotating injection sites and the factors influencing absorption rates.
6. Demonstrate the correct injection technique.
7. Identify the problems that may arise with the pen and the action to be taken.

Resources needed.

Humapen, Insulin delivery device, 3ml cartridge of saline for demonstration purposes, pen needles. Instruction leaflet accompanying the pen device

Stages of the teaching the skill of using the HumaPen insulin delivery device

Time	Stages	Methods/Aids
2 min	Introduction Importance of the skill Learning outcomes	Verbal explanation
3 min	Identification of the equipment	Display Humapen, needles & insulin cartridge. Emphasise important aspects and explain new terms
5 min	**Demonstration.** Stages of loading the pen **Preparation.** • Remove cap and remove cartridge holder • Place cartridge into the holder. • Push lead screw back with cartridge plunger • Attach cartridge holder, Attach needle • Check insulin flow (using an air shot) dial 6 unit and eject into the air. 2 unit air shot prior to each injection **Choosing a site.** • Explain the choice of sites. • Explain injection technique. • Discuss dose. See page • Disposal of needle or re-use of needle	Show the skill at normal speed so that t patient can see a skilled performance. I would be useful for the patient to see th demonstrator self -injecting. Invite questions but keep to the point Repeat demonstration at a slower speed in steps. Make a note of insulin dose to be taken the patient's blood glucose diary
5 min	**Patient technique (supervised practice)**	
5 min	**Discussion** Ensure pt is able to :- • Outline steps in the procedure. • Identify main sources of error • Safely dispose of sharps • Explain care of the equipment	Handouts and Humapen instruction lea accompanying pen device

Employment Fact File

- Outline safety considerations involved in employment.

  The study is attempting to obtain normoglycaemia in patients with diabetes and therefore an increased risk of hypos exists. Practice nurses should assess the patient's job. If they are in a high risk occupation involving heights or machinery then they are not suitable to join this study. Those patients whose job requires a LGV or PCV driving license will lose their license if insulin is commenced and again should be excluded from the study.

  If the patient is randomised to a therapy sequence involving the addition of insulin then they will face employment restrictions. They cannot apply for jobs in the armed forces, police, merchant navy, fire brigade, prison service, deep sea diving, oil rig work, coal face work, truck or bus driving, airline pilot, air traffic control, these occupations have a blanket ban on employing people on insulin. Those whose work involves irregular shift work may also need to discuss the difficulties of attending the study visits and the problems of blood glucose control that may result from irregular eating habits.

Resources available: DUK employment leaflet

Driving Fact File

This information will have been given to the patient when they were diagnosed. For the purposes of the study we need to recap on the DVLA requirements and inform the patient of the requirements should they be randomised to insulin.

- Car driving licenses can be held by people with diabetes.
- If the diabetes is treated by diet alone the patient does not need to inform DVLA.
- The DVLA (Tel 01792 772151) must be told of your diabetes if the treatment changes (e.g. from diet alone to medication or medication to insulin). This is a requirement by law.

Note: this information must be provided and recorded. The decision to follow this advice is the responsibility of the individual concerned.

- Those treated with diet alone or tablets are not subject to licence restrictions (for diabetes). They can retain their 'until aged 70' privilege, but must inform the DVLA of there is any change to treatment.
- License renewal forms are sent automatically before the expiry date. There is no fee for renewal.
- License renewal is granted after completion of the form by the person with diabetes (including signed consent for the individual's doctor to be consulted by the DVLA, if required).
- A medical check may be requested by the DVLA
- Licenses are renewed every 1, 2 or 3 years (depending on health)
- The driver must inform his/her insurance company of the presence of diabetes.
- Some insurance companies load the driver's premium. This should be challenged. It is sensible to 'shop around' because the Disability Discrimination Act 1995 has improved this situation. DUK Trading can also offer motor insurance cover. (information is in the leaflet).

Resources available: DVLA Information Sheet

VISIT 6-8: DOSE OPTIMISATION OF THERAPIES (MONTHS 4-6)

VISITS 6-8

Issue and check completion of quality of life questionnaires

Ask patient to complete these forms in the waiting room prior to their appointment

Check their completion at the beginning of their visit.

Complete CRF 009 – 013 and 021 if adverse events have occurred

Discuss blood glucose monitoring results and diary completion

Troubleshoot any problems that have been experienced so far. Download the meter results.

Perform a clinic capillary glucose sample and take fasting blood tests

Ask the patient to take the capillary sample and check their technique

Ensure the patient has fasted before taking their blood tests

Review adherence with study treatment

Use the adherence fact file.

Adjust dose of basal agent using gating approach.

Add prandial agent unless majority of home glucose values are PPG <8mmol (H GP)

Resources Available: Medication Adjustment fact file

Patients commencing insulin: Arrange weekly appointments for 3 weeks to teach insulin skills and education topics: injections, insulin storage, needle disposal, BG testing, hypos, sick days, driving, emergencies, contact numbers. Prescribe Hypostop, BD safe clip and pen needles.

Patients commencing repaglinide: give drug information

Resources available: Insulin factfile and checklist

Discuss hypoglycaemia and its management

Arrange a fasting appointment for one months time

Ask the patient to fast from midnight and bring their blood glucose diary and meter with them.

Return the copies of all forms and samples to the DTU

VISIT 8-14: GLUCOSE MAINTENANCE (MONTH 6-12)

VISIT 8-14

Issue and check completion of quality of life questionnaires

Ask the patient to complete these forms in the waiting room

Check their completion at the beginning of their visit.

Complete CRF 009 – 014 and 021 if any adverse events have occurred

Discuss blood glucose monitoring results and diary completion

Troubleshoot any problems that have been experienced so far and download the meter

Test the meters using the control solution at visits 8 and 11 and write results in patient's diary

Perform a clinic capillary glucose sample and take fasting blood tests as per ARF

Ask the patient to take the capillary sample and check their technique

Ensure the patient has fasted before taking their blood tests

Check FPG and PPG values for treatment progression using medication adjustment factfile

Issue study prescription for the next period (H GP)

Review adherence and hypoglycaemia management

Arrange a fasting appointment for one months time

Ask the patient to fast from midnight and bring their glucose diary and meter with them.

Return the copies of all forms and samples to the DTU

Appendix 5: Sample Specification

Track	Sample	Collection				Preparation	Storage			
		Tube	Additive(s)	Volume	Label [1]		Tube	Volume	Temperature	Label [1]
#01	Venous blood	5ml vacutainer	Heparin	5ml	#01ALTPH	cold spin @2000g 15 min and transfer plasma	3.5ml Sarstedt	3ml	4°C	#01ALTPH
#02	Venous blood	5ml vacutainer	Heparin	5ml	#02TZDPH	cold spin @2000g 15 min and transfer plasma	3.5ml Sarstedt	3ml	4°C	#02TZDPH
#03	Venous blood	5ml vacutainer	Heparin	5ml	#03CRPH	cold spin @2000g 15 min and transfer plasma	3.5ml Sarstedt	3ml	4°C	#03CRPH
#04	Venous blood	5ml vacutainer	EDTA	5ml	#04BE	None	None	0	4°C	#04BE
#05	Venous blood	5ml vacutainer	EDTA	5ml	#05PE	cold spin @2000g 15 min and transfer plasma	3.5ml Sarstedt	3ml	4°C	#05PE
#06	Urine	Apex	Thiomersal	2ml	#06UA	None			4°C	#06UA
#07	Reserve	10ml vacutainer	EDTA	10ml	#07aPE	cold spin @2000g 15 min and transfer plasma	2ml Sarstedt	1ml	-20°C	#07aPE
					#07bPE		2ml Sarstedt	1ml	-20°C	#07bPE
					#07cPE		2ml Sarstedt	1ml	-20°C	#07cPE
					#07dPE		2ml Sarstedt	1ml	-20°C	#07dPE
#08	Reserve	10ml vacutainer	Heparin	10ml	#08aPH	cold spin @2000g 15 min and transfer plasma	2ml Sarstedt	1ml	-20°C	#08aPH
					#08bPH		2ml Sarstedt	1ml	-20°C	#08bPH
					#08cPH		2ml Sarstedt	1ml	-20°C	#08cPH
					#08dPH		2ml Sarstedt	1ml	-20°C	#08dPH
#09	Venous blood	5ml vacutainer	Fluoride	2ml	#09PF	cold spin @2000g 15 min and transfer plasma	3.5ml Sarstedt	1ml	4°C	#09PF

Approved: ..... Date: ..... Study Coordinator

Appendix 6: Sample Matrix

		Study Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Storage
Track	Assay(s)	Study Month	*0*		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*After Assay*
#01	ALT		X		T	T	T	T	T	T	T	T	T	T	T	X	-20°C
	Creatinine		X													X	-20°C
#02	HbA1c		X		X	X	X	X	X	X	X	X	X	X	X	X	Not stored
#03	Cholesterol		X													X	-20°C
	HDL		X													X	-20°C
	LDL		X													X	-20°C
	VLDL		X													X	-20°C
	Triglyceride		X													X	-20°C
#04	Urine albumin		X													X	-20°C
#05a	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#05b	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#05c	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#05d	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#06a	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#06b	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#06c	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#06d	Reserve		X		X	X	X	X	X	X	X	X	X	X	X	X	-70°C
#07	FPG		X		X	X	X	X	X	X	X	X	X	X	X	X	Not stored
#08	FBC		X							X						X	Not stored

Appendix 7: Sample Case Report Form

Glycaemic Optimisation Outcomes in Diabetes (Study No:C00.008)

CRF: 0 1 9 Subject: ☐-☐☐☐-☐☐☐-☐ Visit : ☐☐☐

Initials: ☐☐☐ Date: ☐☐ / ☐☐ / ☐☐☐☐

YOUR DIABETES TREATMENT

These questions are concerned with your diabetes treatment (including diet, tablets ar insulin) over the past few weeks. Please circle a number on each scale.

1. How satisfied are you with your current treatment?
   very satisfied 6 5 4 3 2 1 0 *very dissatisfied*

2. How often have you felt that your blood sugars have been unacceptably high recently?
   most of the time 6 5 4 3 2 1 0 *none of the time*

3. How often have you felt that your blood sugars have been unacceptably low recently?
   most of the time 6 5 4 3 2 1 0 *none of the time*

4. How convenient have you been finding your treatment to be recently?
   very convenient 6 5 4 3 2 1 0 *very inconvenient*

5. How flexible have you been finding your treatment to be recently?
   very flexible 6 5 4 3 2 1 0 *very inflexible*

6. How satisfied are you with your understanding of your diabetes?
   very satisfied 6 5 4 3 2 1 0 *very dissatisfied*

7. Would you recommend this form of treatment to someone else with diabetes?
   Yes, I would definitely recommend the treatment 6 5 4 3 2 1 0 *No I would definitely not recommend the treatment*

8. How satisfied would you be to continue with your present form of treatment?
   very satisfied 6 5 4 3 2 1 0 *very dissatisfied*

Please make sure that you have circled one number on each of the scales

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Appendix 8: Miscellaneous Results

Table A8.1: Adverse Events

Adverse Event	Therapy	Related	Month	Duration (days)	Days Lost	SAE
Abdominal bloating*	E	Yes	2	56	0	No
Abdominal pain	A	Yes	5	285	0	No
Abdominal pain	B	Yes	2	12	0	No
Abdominal pain*	B	Yes	4	27	0	No
Angina exacerbation*	D	Yes	3	23	0	No
Ankle oedema	C	Yes	2	39	0	No
Ankle oedema	D	Yes	2	97	0	No
Ankle oedema*	D	Yes	2	28	0	No
Ankle oedema	E	No	3	69	0	No
Ankle oedema	F	No	8	13	0	No
Apthous ulcers	E	No	8	19	0	No
Arthralgia	F	No	6	28	0	No
Arthralgia*	D	Yes	2	33	0	No
Asthma exacerbation	E	No	7	31	0	No
Asthma exacerbation	A	No	2	6	0	No
Back pain	B	No	4	1	0	No
Back pain	B	No	6	189	0	No
Claudication pain	F	No	6	50	0	No
Conjunctivitis	F	No	9	7	0	No
Constipation	C	No	1	32	0	No
Cystitis (recurrent)	B	Yes	4	58	0	No
Diarrhoea*	A	Yes	2	11	0	No
Diarrhoea	A	Yes	4	3	0	No
Diarrhoea	A	Yes	9	155	0	No
Diarrhoea	B	Yes	1	19	0	No
Diarrhoea	B	Yes	3	276	0	No
Diarrhoea*	B	Yes	4	210	0	No
Diarrhoea	B	No	10	14	10	No
Diarrhoea	F	Yes	4	28	0	No
Diarrhoea	F	Yes	10	160	0	No
Dizziness	F	Yes	2	7	0	No
Fatigue	C	Yes	1	8	0	No
Fatigue	D	Yes	2	33	0	No
Flatulence	F	Yes	4	29	0	No
General malaise	B	Yes	6	2	0	No
General malaise	E	Yes	3	2	0	No
Grade 4 hypo*	D	Yes	4	1	1	Yes
Groin pain	B	No	11	22	1	No
Headache	A	No	8	3	0	No
Hyperglycaemia	F	Yes	3	22	0	No
Hypothyroidism	B	No	11	38	0	No
Leg pain	F	No	3	104	0	No
Leg ulceration	A	Yes	9	159	0	No

Numbness/Paraesthesia	A	Yes	7	104	0	No
Parotidectomy	B	No	3	1	1	No
Rash	B	No	2	162	0	No
Shoulder pain	D	Yes	2	8	0	No
Tonsillitis	D	No	4	16	0	No
URTI	A	No	7	14	0	No
URTI	A	No	9	9	0	No
URTI	B	No	2	11	0	No
URTI	B	No	8	9	0	No
URTI	C	No	5	14	0	No
URTI	C	No	6	4	0	No
URTI	D	No	2	5	0	No
URTI	D	No	3	11	0	No
URTI	D	No	5	8	0	No
URTI	E	No	6	4	0	No
URTI	E	No	7	16	0	No
URTI	F	No	3	11	0	No
URTI	F	No	7	11	0	No
Weakness	F	Yes	2	35	0	No
Weight gain	D	Yes	2	64	0	No

*Withdrawn from the study as a result of adverse event