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Identification, Investigation and Management of Patients with Diabetic Nephropathy at the Primary and Secondary Care Interface

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Thesis presented for the degree of Philosophiae Doctor 2007

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Publications

The following publications have arisen directly from the work presented in this thesis

Craig KJ, Donovan K, Munnery M, Owens DR, Williams JD, Phillips AO. **Identification and management of diabetic nephropathy in the diabetes clinic.** Diabetes Care. 2003, 26(6); 1806-1811.

Craig KJ, Williams JD, Riley SG, Smith H, Owens DR, Worthing D, Cavill I, Phillips AO.
Anemia and diabetes in the absence of nephropathy. Diabetes Care. 2005, 28(5); 1118-23.

Craig KJ, Riley SG, Thomas B, Penney M, Donovan KL, Phillips AO.
The impact of an out-reach clinic on referral of patients with renal impairment. Nephron Clinical Practice. 2005; 101(4): 168-173.

Summary of Thesis

Approximately 170 million individuals worldwide have been diagnosed with Diabetes Mellitus and between 85-90% of the total population have Type 2 Diabetes Mellitus. Health care is facing an epidemic not only of Diabetes Mellitus but also of the consequence of the attendant morbidity including macro and micro diseases of the vascular system. Of particular interest for the purposes of this thesis, is the progression to nephropathy and development of cardiovascular risk of a proportion of this population and the investigation of strategies that may slow the decline to end stage renal failure and the need for renal replacement therapy or premature death due to cardiovascular disease.

Initially, screening practice for microalbuminuria was altered, with patients being identified during their clinic visit, rather than retrospectively. In addition, data on blood pressure levels and antihypertensive agents prescription was collected and collated.

Subsequently, a nurse specialist optimised the risk factor management of a cohort of patients with Diabetic Nephropathy using an algorithm driven evidenced based approach.

Finally, analysis was undertaken of the factors that might contribute to the development of anaemia in diabetic nephropathy and hence to increased cardiovascular risk.

The work described in this thesis demonstrates the inherent complexities of dealing with a problem that involves the maintenance of health within a system that has been set up primarily to deal with the consequences of illness.

1.1 Aims

The overall aim of the work presented in this thesis is the examination of a cohort of patients with diabetes, in particular the screening and identification for diabetic nephropathy and the subsequent management of the renal and cardiovascular disease of those identified as being at risk. The impact of the introduction of a nurse specialist to establish evidence-based best practice for screening and hypertension treatment was evaluated and the impact of the change of practice measured against previous historical data.

Following this, a cohort of diabetic patients without nephropathy were evaluated to establish whether factors could be identified that might contribute to the development of anaemia in the early stages of the disease process and before the development of nephropathy.

1.2 Diabetes Mellitus

1.2.1 Definition

The term Diabetes Mellitus describes a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. The abnormalities of metabolism are due to deficient action of insulin on target tissues resulting either from insensitivity to or lack of insulin. In their review of 1999 the World Health Organisation recommended that the terms "insulin-dependent diabetes mellitus" and "non-insulin-dependent diabetes mellitus" and their acronyms "IDDM" and "NIDDM" no longer be used. [2] These terms have led to confusion, as the classification was treatment based rather than pathogenesis based.

1.2.2 Classification

The World Health Organisation report of 1999 classified Diabetes Mellitus into the following categories

Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus (formerly known as 'insulin-dependent diabetes) is an autoimmune T cell mediated disease process caused by the destruction of the β cells of the pancreas and leading to absolute insulin deficiency. The incidence of Type 1 Diabetes Mellitus varies considerably worldwide, with Scandinavia having the highest incidence for example, Finland has an incidence of 35 cases per 100,000 per year) in contrast to Japan and China where the incidence is between 1 to 3 cases per 100,000 per year and Northern Europe and the United States where the rate is between 8 to 17 cases per 100,000 per year [3].

Age at diagnosis most frequently is around 11 years of age in females and 14 years in boys, with no gender differentiation in numbers diagnosed. In addition, it is believed that there are both genetic and environmental factors involved in the susceptibility for the development of Type 1 Diabetes Mellitus.

Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus has replaced the term 'Non Insulin Dependent Diabetes' the latter term causing confusion, as many Type 2 diabetics require insulin to control their hyperglycaemia.

Type 2 Diabetes Mellitus affects about 2 per cent of the Caucasian population in the western world. The prevalence rises with age, reaching around 10% in the population over 70 years of age [4]. The prevalence of Type 2 Diabetes Mellitus is highest in some Pacific islands, intermediate in countries such as India and the United States, and relatively low in Russia and China [3]. This variability is thought to be due to genetic, behavioural, and environmental factors [4].

The young and middle-aged of Asian or Afro Caribbean extraction who live in western cultures have an increased prevalence of around 5% or more [5]. Age at diagnosis has most commonly been around 40 years rising to a peak at around 60 to 65 years, however, recent reports have highlighted the incidence of childhood obesity which has resulted in up to one third of Americans under 20 years diagnosed with diabetes, having Type 2 disease.

It is thought that Type 2 diabetes is due to a combination of insulin resistance and a decrease in insulin secretion [1]. Susceptibility is thought to be determined by both genetics and environment. The lifetime risk for a first-degree relative of a patient with type 2 diabetes is five to ten times higher than that of age- and weight-matched subjects without a family history of diabetes [6] but even among groups with increased genetic risk for diabetes, environmental factors play a major role in the development of diabetes. For

example, the prevalence of diabetes among Pima Indians in Mexico (6.9 per cent) is less that one-fifth that of Pima Indians (38 per cent) living in the United States [7]

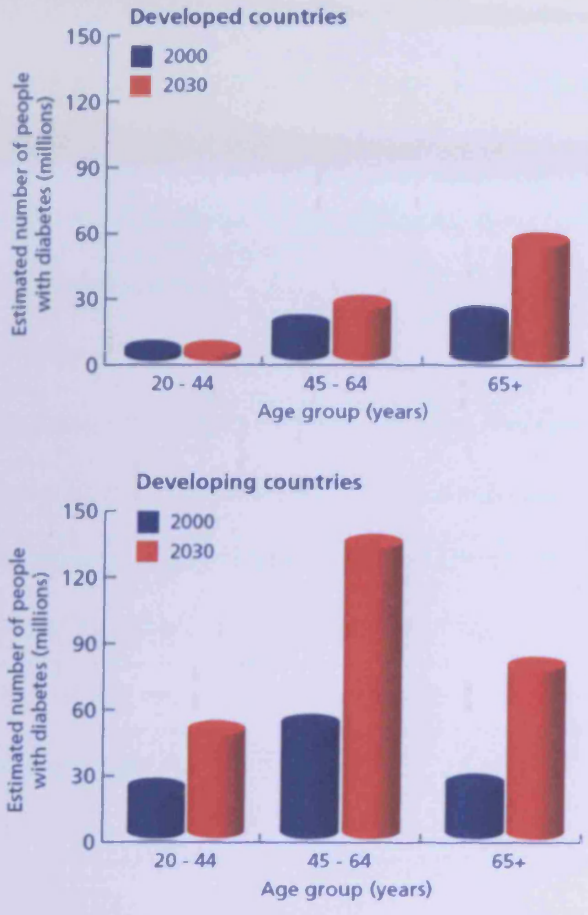
In addition to these two main types of diabetes, there are two other types of diabetes mellitus, namely specific and gestational, which will not be discussed in detail as part of this thesis.

1.2.3 Prevalence of Diabetes Mellitus

The World Health Organisation estimated recently that there were 171 million individuals worldwide with diabetes. It is projected that by the year 2030 this number will have increased to 366 million [8]

Although diabetes is regarded by some as a disease of the developed world, the projected rise in prevalence is most marked amongst individuals in the developing world between the ages of 45-60 years. (Figure 1)

Figure 1: Projected numbers of individuals with diabetes by 2030 in the developed and developing world



Estimated number of adults with diabetes.

Adapted from: Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Wild S, Roglic G, Green A, Sicree R, King H Diabetes Care 27:1047–1053, 2004 [8]

1.2.4 Comorbid complications of Diabetes Mellitus

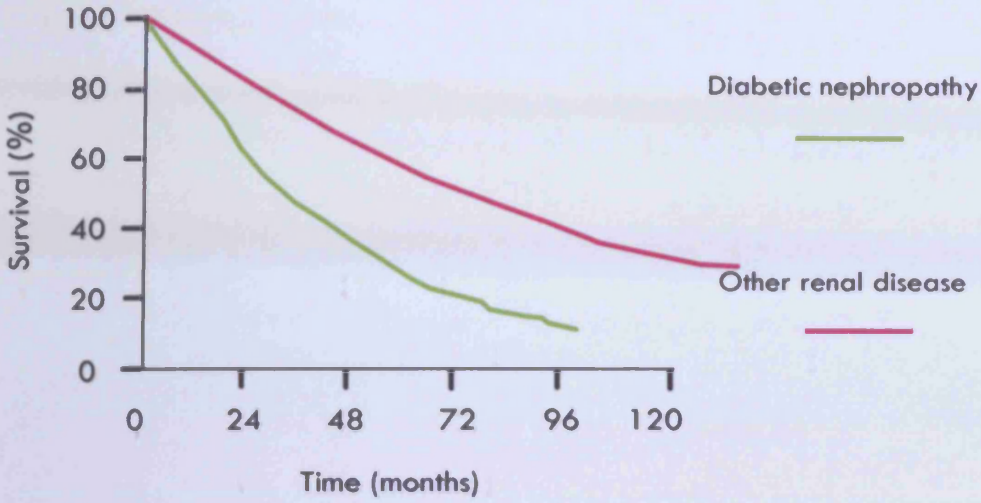
The proportion of individuals suffering from Type 2 Diabetes Mellitus is between 85-90% of the total diabetic population worldwide and health care is facing an epidemic not only of Diabetes Mellitus but also of the consequence of the attendant morbidity. There are many comorbid complications of Type 2 Diabetes Mellitus including macro and micro diseases of the vascular system such as ischaemic heart disease, peripheral vascular disease, retinopathy and nephropathy.

In view of this and the levels of mortality if this patient group progress to requiring renal replacement therapy, the remainder of this thesis will focus on Type 2 Diabetes Mellitus and its consequences, in particular the management of cardiovascular disease and nephropathy given the direct relationship that exists between decreased Glomerular Filtration Rate (GFR) as a risk association with cardiovascular disease (CVD) and the fact that for patients with end stage renal disease (ESRD), the major cause of death is CVD.

1.3 Survival of patients with Type 2 Diabetes Mellitus on Renal Replacement Therapy

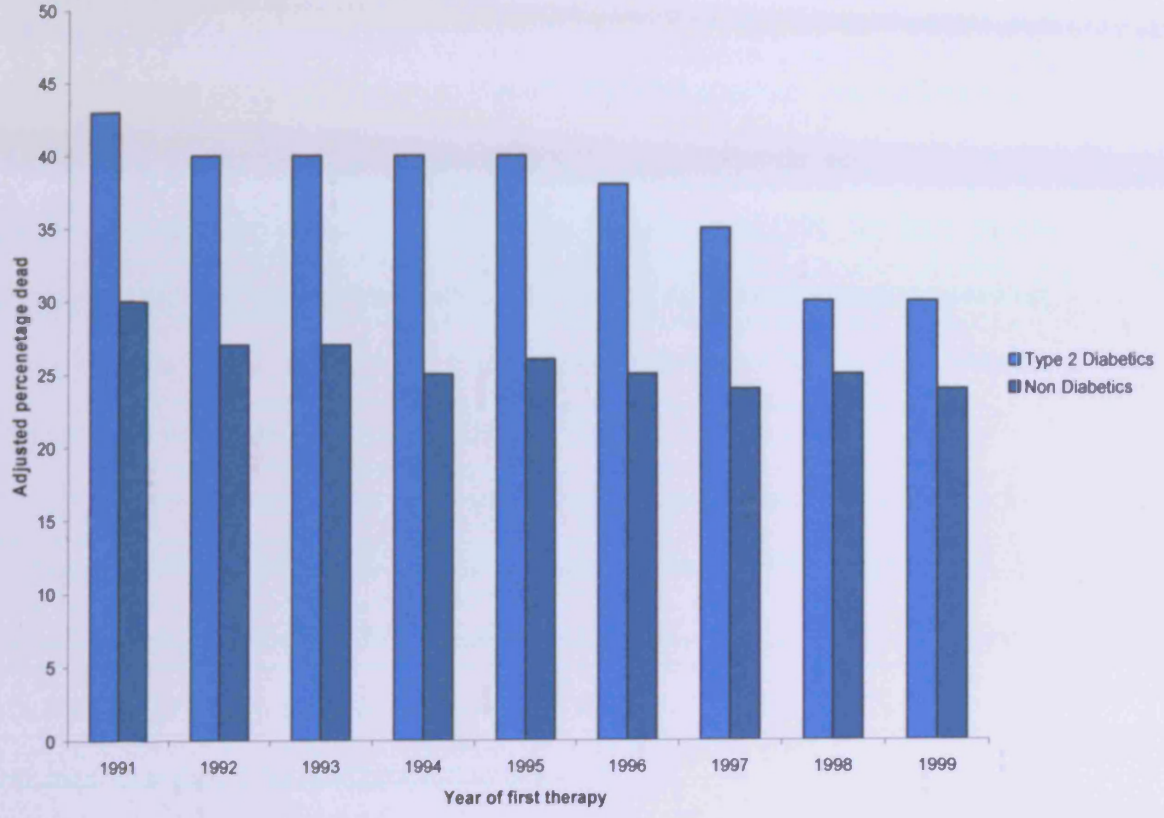
The importance of prevention of development of nephropathy in patients with Type 2 Diabetes Mellitus is emphasised by the prognosis of individuals who progress to the requirement for renal replacement therapy. In contrast to individuals with other renal diseases, patients with diabetic nephropathy have significantly worse survival (Figure 2) and although survival on dialysis in general has improved over time, as technology and techniques have improved, the differences between diabetic and non-diabetic patients have remained (Figure 3).

Figure 2: Prognosis of diabetic patients on dialysis



Adapted from: Marcelli et al; Prognosis of diabetic patients on dialysis: Data from the Lombardy Registry, Nephrology Dialysis and Transplantation 1995 Oct, 10: 1895-1900 [9]

Figure 3: European two year death rates among dialysis patients with Type 2 diabetic End Stage Renal Disease versus nondiabetic (adjusted for the age, gender and country distribution of incident patients in 1999)



Adapted from: Van Dijk PCW, Jager KJ, Stengel B, Gronhagen-Riska, C, Feest TG, Briggs JD. Renal Replacement Therapy for diabetic end-stage renal disease: Data from 10 registries in Europe (1991-2000). Kidney International 67;1489-1499, 2005 [10]

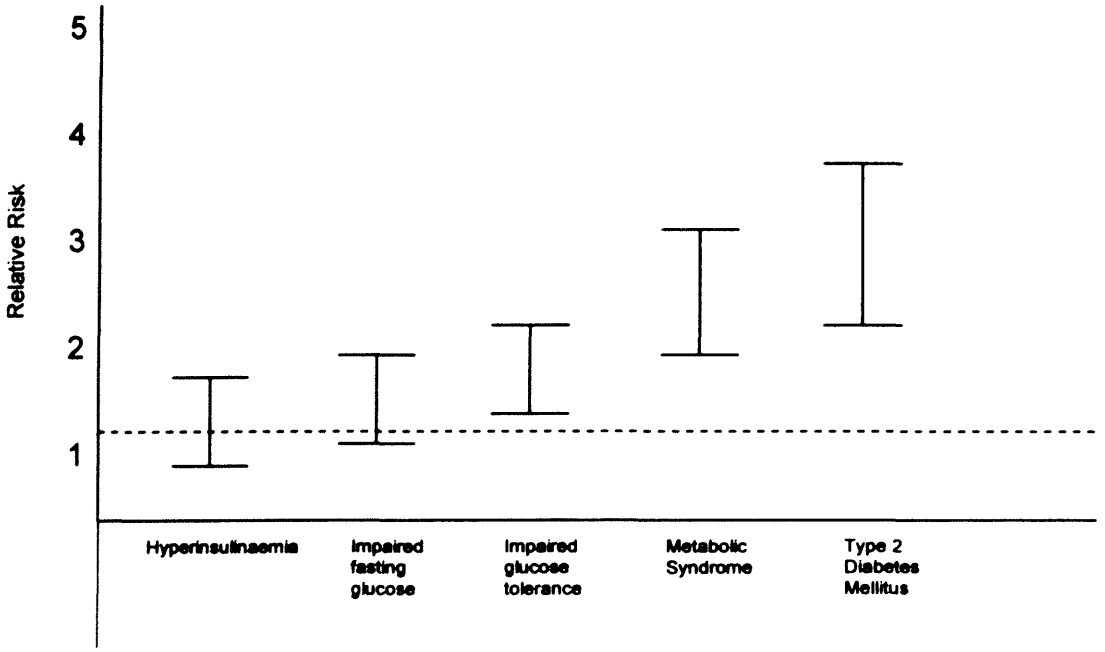
1.4 Cardiovascular disease and Type 2 Diabetes Mellitus

Epidemiological studies have shown increased rates of Coronary Heart Disease (CHD), angina, myocardial infarction (both fatal and non-fatal) and sudden cardiac death amongst patients with diabetes [11] . The spectrum of diabetic disease has been described as a range from hyperinsulinaemia and impaired fasting glucose through to Type 2 diabetes mellitus. Increased risk of CVD does not start with Type 2 diabetes but rather extends across the entire spectrum of diabetic disease. A review by Tziakis et al [12] in 2005 of the cardiovascular risk across this diabetic syndrome documented a progressively increasing risk of cardiac events from hyperinsulinaemia to Type 2 diabetes as illustrated in Figure 4.

Type 2 Diabetes Mellitus has been shown to be associated with a two to four fold increased risk of coronary heart disease [13] and individuals with Type 2 Diabetes Mellitus without CVD have the same risk of CHD as non diabetic individuals with a previous history of CVD.[13] In addition, women with diabetes lose their inherent protection against CVD.

Data from the Finnish Multinational monitoring of Trends and determinants of Cardiovascular Disease showed that the mortality rate for patients with Type 2 diabetes who suffer a myocardial infarction was increased by 25%, a rate for out-of–hospital mortality rate which was increased by 25% and a one year mortality rate increased by 97%[14].

Figure 4: Progressive relative risk for cardiac events



Values represent reported 95% confidence intervals for relative risk in epidemiological studies

From: Tziakas, DM; Chalikias, GK and Kaski, JC. Epidemiology of the diabetic heart, Coronary Artery Disease, November 2005, 16 (1) S3-S1

The impact of cardiovascular disease in Type 2 diabetes is highlighted by the fact that 65 percent of all the deaths of patients with Type 2 diabetes are due to cardiovascular disease.

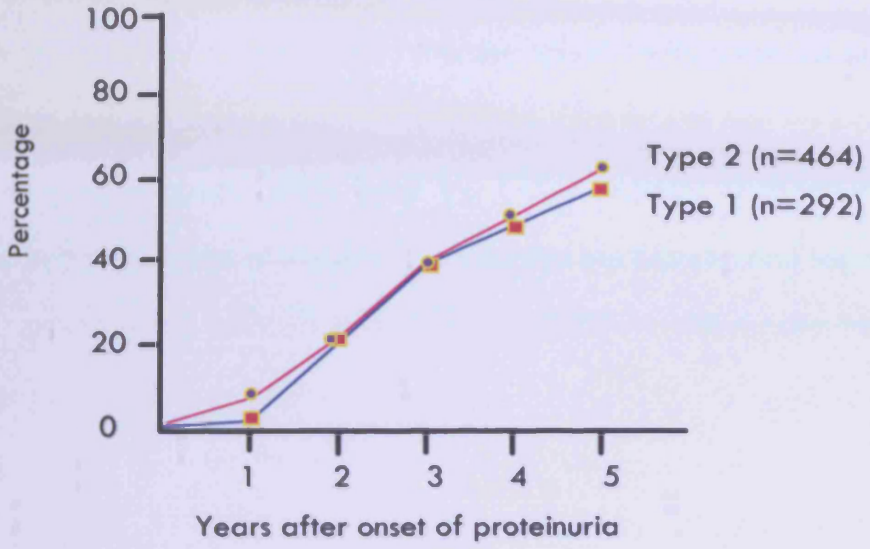
Strategies to delay or prevent the development of or improve the management of cardiovascular disease and its attendant additional comorbidity, including anaemia in this high risk group form the basis of the studies undertaken and reported here.

1.5 Nephropathy and Type 2 Diabetes Mellitus

Previously, the risk of developing comorbidity, such as nephropathy, was believed to be significantly lower for patients with Type 2 diabetes than for those with Type 1 disease. However, studies now confirm that the risk is similar and that the timelines for development of renal failure and the rate of decline in GFR are comparable [15] [16] (Figure 5).

The incidence of end stage renal failure caused by diabetic nephropathy is increasing worldwide although this overall figure masks the fact that some commentators have reported a decline in the incidence of Type 1 nephropathy. Data reported from Sweden, in 1994, compared patients diagnosed in the 1960s with those from the 1990s and demonstrated a significant decline in the incidence of persistent albuminuria from 30 to 8.9%. [17]. The authors hypothesised that this decline might be due to improved glycaemic control in the more recent cohort, but it has not been possible to replicate this finding in other centres. What is certainly in no doubt is the increasing incidence and prevalence of nephropathy in patients with Type 2 diabetes, with diabetes being the most common cause of end stage renal failure world wide [4].

Figure 5: Cumulative prevalence of renal failure in Types 1 and 2 Diabetes Mellitus



Adapted from Hasslacher C, Ritz E, Wahl P, Michael C. Similar risks of nephropathy in patients with Type I or Type II diabetes mellitus. Nephrology Dialysis Transplantation. 1989;4:859-63. [18]

The changing impact of diabetes as the primary renal diagnosis in patients presenting for renal replacement is clear when reviewing registry data from the European Dialysis and Transplant Association (EDTA). The EDTA noted in 1974, that diabetic nephropathy is one of the 'rarer causes' of presentation and acceptance for renal replacement therapy and in 1975, it was included for the first time as a separate entity for reporting purposes and had an incidence of around three percent. Since then, the EDTA registry changes in both incidence and prevalence of diabetic nephropathy are marked and reported in Table 1, although the collated data masks significant differences between countries.

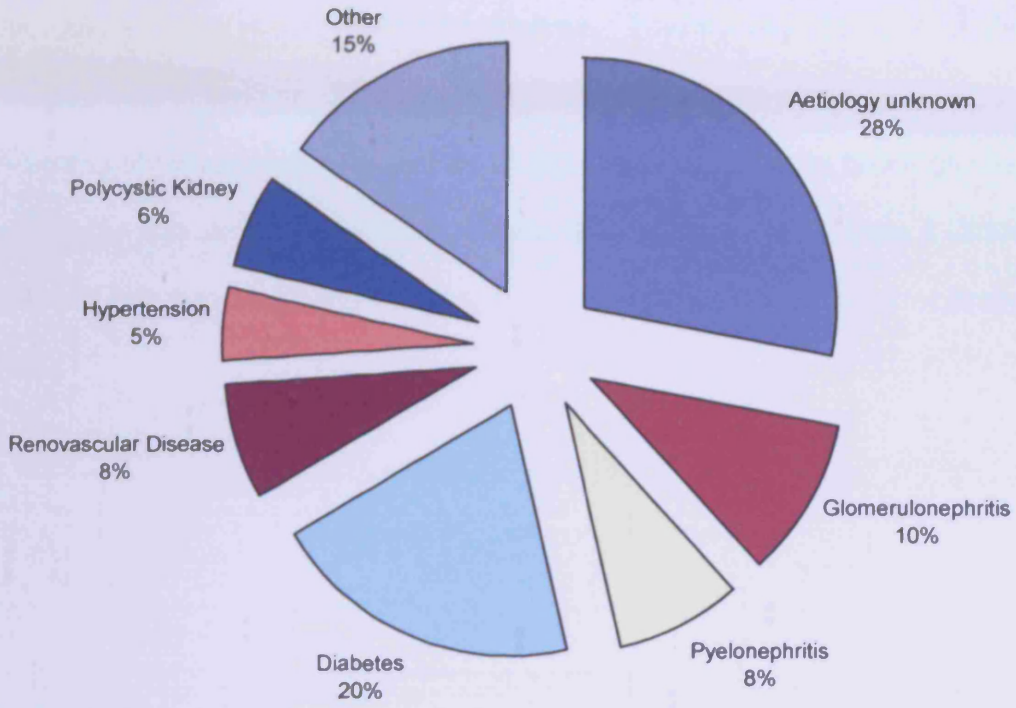
Table 1: European Crude Incidence and Prevalence for Diabetic and Non Diabetic Renal Disease (pmp)

Incidence (95% CI)	Type 2 Diabetic Nephropathy	Non-Diabetic Renal Disease
1991-1992	7.1 (6.6-7.5)	67.8 (66.4-69.2)
1999-2000	17.9 (17.2-18.6)	93.8 (92.2-95.3)
Prevalence (95% CI)	Type 2 Diabetic Nephropathy	Non-Diabetic Renal Disease
1991-1992	15.7 (15.0-16.3)	455.8 (452.2-459.4)
1999-2000	44.5 (43.5-45.6)	607.2 (603.2-611.2)

Adapted from: Van Dijk PCW, Jager KJ, Stengel B, Gronhagen-Riska, C, Feest TG, Briggs JD. Renal Replacement Therapy for diabetic end-stage renal disease: Data from 10 registries in Europe (1991-2000). Kidney International 67;1489-1499, 2005 [10]

Changes in the underlying diagnosis of individuals presenting for renal replacement therapy (RRT) over the last twenty years are also highlighted in data from the United States Renal Data System where, in the 1980s, diabetic nephropathy comprised 28% of the RRT population and by 2006 this rate had risen to over 50% and was the most common presenting diagnosis[19]. Data from the most recent UK Renal Registry report has highlighted the impact of diabetic nephropathy in patients starting renal replacement therapy and is described in Figure 6 [20] .

Figure 6: Primary Renal Diagnosis of patients starting Renal Replacement Therapy: UK 2006



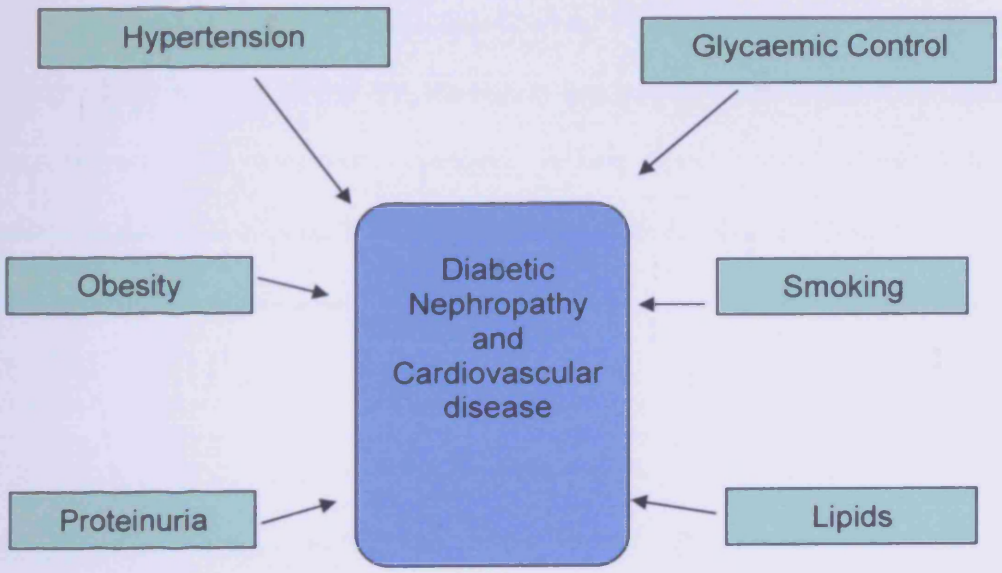
Adapted from: Ansell D, Feest TG, Tomson C, Williams AJ, Warwick G, UK Renal Registry Report 2006, UK Renal Registry, Bristol , UK

The increase in the numbers of individuals being diagnosed with Type 2 Diabetes Mellitus at an early age has caused a commensurate increase in the numbers of individuals exposed to longer time scales of hyperglycaemia. Changes in the lifestyle of young adults predispose them to obesity and along with lack of regular exercise leads to a subsequent increase in susceptibility for developing Type 2 Diabetes Mellitus. Traditionally Type 2 Diabetes Mellitus was a disease of the elderly and as more individuals live longer the numbers at risk are increasing. Part of this increase is due to better glycaemic and blood pressure control which means that individuals with Type 2 Diabetes Mellitus are surviving long enough to develop the complications of diabetes [15].

1.6 Development of cardiovascular disease and nephropathy

The development of cardiovascular disease and nephropathy in patients with Type 2 diabetes has been linked with a number of shared risk factors which are illustrated in (Figure 7). Of particular interest in terms of disease management are those factors which are capable of modification

Figure 7: Factors contributing to development of Cardiovascular Disease and Nephropathy in Type 2 Diabetes Mellitus:



1.6.1 Glycaemic control and the development of cardiovascular disease and nephropathy

It remains a matter of discussion whether increased cardiovascular risk in patients with diabetes mellitus is associated with or caused by hyperglycaemia. Analysis of data from the UKPDS [21] established a linear relationship between increased HbA_{1c} levels and the risk of fatal or non-fatal myocardial infarction (MI), fatal or non-fatal stroke, amputation or death from peripheral vascular disease and heart failure. After 10 years, the obtained HbA_{1c} in the intensive group was 7.0% versus 7.9% in the conventional group. [22]. This small difference in HbA_{1c} was associated with a 16% decreased risk for MI but this trend in reduction in macrovascular events did not reach statistical significance at the 5% level and the risk of diabetes related death or all-cause mortality was not changed. It has been hypothesised that the inability to prove the benefit of improved glycaemic control on macrovascular endpoints in this study may have resulted from the small achieved difference in $HbA1_c$.

It has been demonstrated in Type 1 Diabetes Mellitus that intensive control of blood glucose levels, reduce the proportion of patients developing diabetic nephropathy. The Diabetes Control and Complications Study [23] was designed to investigate whether Intensive Therapy (IT) when compared to Conventional Therapy (CT) would affect the risk of onset and progression of complications. The risks of the microvascular complications over the average of 6.5 years of follow-up were reduced by 26-63% with intensive versus conventional therapy. The IT group achieved a median HbA_{1C} throughout the

study of 7.2% *vs.* 9.1% in the CT group ($p<0.001$). Early renal damage, the appearance of microalbuminuria (defined as Albumin Excretion Rate (AER) > 40 mg/24 hours) was reduced by 60%. In addition, clinically significant renal damage (defined as Albumin Excretion Rate (AER) of > 300 mg/24 hours) was reduced by 54%.

Hyperglycaemia may produce end organ damage in the kidney both by direct effects on kidney tissue or by the stimulation of substances which have an effect on specific components of the kidney. These substances include hyperglycaemic induced activation of protein kinase C and subsequent increases in levels of Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor -Beta (TGF-Beta) which in the case of VEGF leads to changes in vascular permeability and angiogenesis [24] [25] [26] and in the case of TGF-Beta stimulates collagen production leading to fibrosis [27] [28].

In addition to activation of the protein kinase C pathway, hyperglycaemia activates the renin-angiotensin system, thereby contributing to the development of cardiovascular disease and diabetic nephropathy. The production of substances capable of modifying the action of the renin-angiotensin system have provided the main therapeutic option in the slowing of progression of diabetic nephropathy.

1.6.2 Hypertension and the development of cardiovascular disease and nephropathy

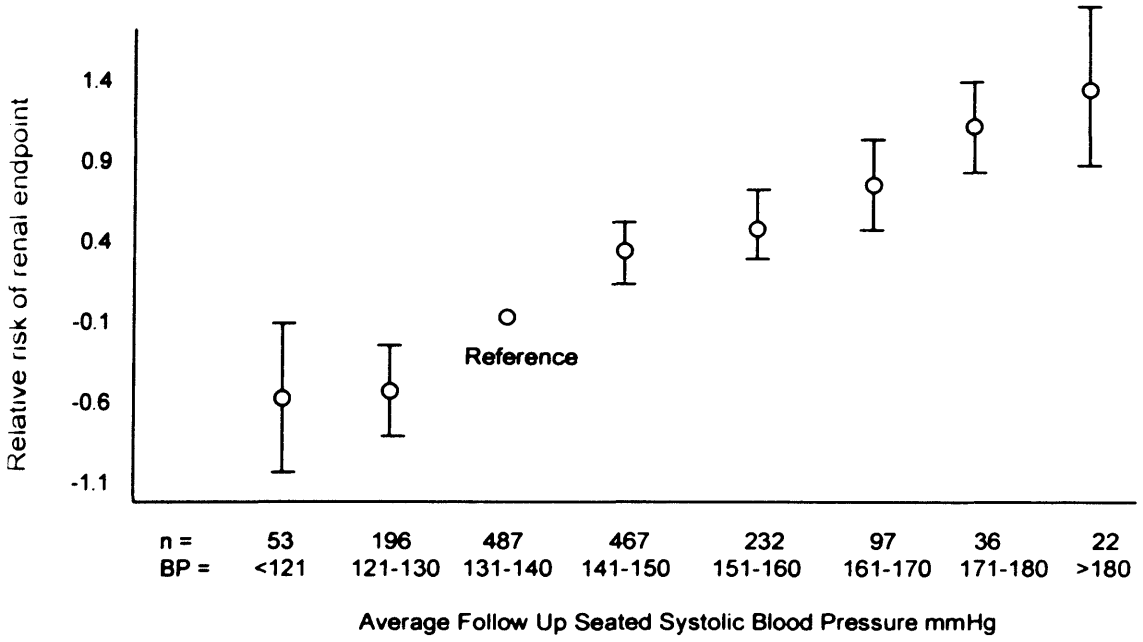
Hypertension is present in large numbers of patients with Type 2 diabetes at diagnosis. One study of over 3500 newly diagnosed patients found that thirty nine percent were already hypertensive [29]. Hypertension was strongly associated with obesity and an increased risk for cardiovascular morbidity and mortality.

An increase in left ventricular mass is a common occurrence in hypertension. This left ventricular hypertrophy (LVH) is associated with an increased risk of cardiovascular events such as angina, myocardial infarction, stroke, heart failure and sudden death [30], [31], [32]. In addition, it has been reported that there is a higher incidence of ventricular arrythmias in patients with LVH when compared with those without LVH [33]. The importance of LVH as a risk factor for cardiovascular events and the progression of kidney disease was confirmed in the RENAAL study where LVH was associated with the primary composite endpoint of doubling of serum creatinine, End Stage renal disease (ESRD) or death (hazard ratio=1.44, p=0.011) [34]. In the same study, LVH was also associated with the composite end point of doubling of serum creatinine and ESRD (hazard ratio=1.42, p=0.031) as well as cardiovascular events (hazard ratio=1.68, p=0.001). The impact of anaemia in the development of LVH has been well documented in ESRD and in addition it has been observated by Ritz and others that the onset of anaemia in patients with Type 2 diabetes is more precipitous and the degree of anaemia is more than would be expected with levels of GFR than in patients with other causes of ESRD.

The role of hypertension in the development of nephropathy is best understood by analysis of the impact of correction of hypertension on the progression of diabetic renal disease. Current data suggests that blockade of the Renin-Angiotensin-Aldosterone system (RAAS) and the subsequent decrease in blood pressure is effective in patients with Type 2 diabetes [35], [36], [37]. There remains controversy over the most appropriate blood pressure target although evidence from a large randomised double blind trial found that an achieved Systolic Blood Pressure(SBP) >149 mmHg was associated with a 2.2-fold increase in the risk for doubling serum creatinine compared with SBP<134 mmHg [38]. Progressive lowering of SBP to 120 mmHg was associated with improved renal and patient survival, an effect independent of baseline renal function. Below this threshold, all-cause mortality increased. An additional renoprotective effect of irbesartan, independent of achieved SBP, was observed down to 120 mmHg. There was no correlation between diastolic BP and renal outcomes. These investigators recommended a SBP target between 120 and 130 mmHg, in conjunction with blockade of the renin-angiotensin system, in patients with Type 2 diabetic nephropathy, although others have urged caution in lowering the diastolic pressure below 60mmHg as there exists an increased risk of cardiac events, particularly in those with coronary artery disease. The relative risk of the renal endpoint (doubling of serum creatinine) in relation to achieved systolic blood pressure is illustrated in Figure 8.

The choice of drug therapy to achieve reductions in blood pressure will be discussed in greater detail in the section on prevention.

Figure 8: Relative risk of doubling of serum creatinine with achieved systolic blood pressure



Pohl M, Blumenthal S, Cordonnier D, De Alvaro F, DeFerrari G, Eisner G, et al. Independent and Additive Impact of Blood Pressure Control and Angiotensin II Receptor Blockade on Renal Outcomes in the Irbesartan Diabetic Nephropathy Trial: Clinical Implications and Limitations. Journal of the American Journal Society of Nephrology. 2005;16: :3027-37

1.6.3 Obesity and the development of cardiovascular disease and nephropathy

Obesity is a chronic metabolic disorder associated with cardiovascular disease and increased morbidity and mortality. Alterations in cardiac structure and function occur as adipose tissue accumulates both with or without the presence of hypertension. As a result of the metabolic needs of this excess tissue, circulating blood volume, plasma volume, and cardiac output all increase. The increase in blood volume in turn increases venous return to the ventricles, eventually producing dilatation and left ventricular hypertrophy. Systemic hypertension, pulmonary hypertension (left ventricular failure, chronic hypoxia) and CHD all occur with disproportionately high frequency in obese individuals and may cause or contribute to alterations in cardiac structure and function. There is also an increased risk of sudden cardiac death in obesity [39].

The benefits of weight reduction on the cardiovascular system have been well documented and include

- Decreased blood volume
- Decreased cardiac output
- Decreased left ventricular mass

Adapted from Poirier et al [39].

It has been shown that a high body mass index (BMI) is associated with an increased incidence of nephropathy [40] [41] and weight loss may reduce proteinuria and improve kidney function [42] [43] . However the effect of obesity in these studies has not been demonstrated independently of glycaemic control.

It is evident however from all of these studies detailed above that the development of diabetic nephropathy is multifactorial and that currently none can be singled out as being the most important in the assessment of an individual's risk of developing nephropathy.

1.6.4 Smoking and the development of cardiovascular disease and nephropathy

Cigarette smoking increases all-cause and cardiovascular mortality [44] [45] In the study by Qiao et al [44], the adjusted hazard ratio for 35 year all-cause and cardiovascular mortality was 1.62 and 1.63, respectively for current smokers compared to nonsmokers. In addition, those who persisted in smoking cessation had no increased risk of death compared to nonsmokers

Studies in individuals with Type 2 diabetes have highlighted that there is a higher incidence of smoking amongst the patient group with microalbuminuria and that for smokers, the progression from micro to macro albuminuria and the time from macroalbuminuria to End Stage Renal Disease and the time from End stage Renal Disease to death is shortened [46].

Studies have shown that cigarette smoking causes a decrease in GFR in diabetic patients with normal or near-normal renal function, independent of

confounding factors including severity of proteinuria. The latter finding suggests a mechanism independent of glomerular damage [47].

1.6.5 Albuminuria and the development of cardiovascular disease and nephropathy

Microalbuminuria has been associated with increased cardiovascular mortality in populations of both diabetic and nondiabetic subjects [48] [49] [50]. It has also been used as a marker of cardiovascular disease and it has been hypothesised that microalbuminuria is a marker of generalised endothelial dysfunction.

In survivors of myocardial infarction, both albuminuria and the transvascular escape rate of albumin are increased [51]. Albuminuria has also been shown to predict the severity of atherosclerosis [52], [53].

The relative contribution of underlying vascular disease as opposed to diabetic nephropathy towards albuminuria is not clear. However, there is evidence to suggest that microalbuminuria is an indicator of both micro- and macrovascular disease.

In general, proteinuria is regarded as a marker of damage to the glomerulus but recent studies have shown that it may also contribute to renal and cardiovascular dysfunction in its own right. In animal models, proteinuria has been linked to increased interstitial inflammation [54] while Parving and colleagues [55] showed that rates of decline of GFR were double in patients with the highest rates of microalbuminuria in comparison to that of those with the lowest rates of albumin excretion. Data from some studies suggest that progression of renal disease is not related to the level of proteinuria but rather

to the underlying degree of renal injury and this has led to the assertion that this is a self –fulfilling hypothesis, in that those with the most severe renal disease are most likely to have the worst proteinuria and the most precipitous decline in renal function [56].

Data from de Zeeuw and his colleagues has shown that the short-term-induced antiproteinuric effect of ACE Inhibitors and /or Angiotensin Receptor Blockers appears to predict the long-term cardiovascular and renal protection in that; the more albuminuria is lowered, the more that the individual is protected. The authors state that these data suggest that albumin is not only a risk marker for cardiovascular and or renal disease, but it may also be a useful target for therapy [57]. In addition, further studies have demonstrated that across all categories of Systolic Blood Pressure change, a progressively lower ESRD hazard ratio was observed with a larger albuminuria reduction and a lower residual level of albuminuria was also associated with lower ESRD risk [58]. In microalbuminuric subjects, treatment with fosinopril had a significant effect on urinary albumin excretion. In addition, fosinopril treatment was associated with a trend in reducing cardiovascular events [59].

Daily aspirin intake reduced vascular events by about 25 percent in patients who had previous myocardial infarction, stroke, transient ischemic attack, or cardiovascular disease; patients with diabetes had risk reductions comparable to those of nondiabetic patients [60] .

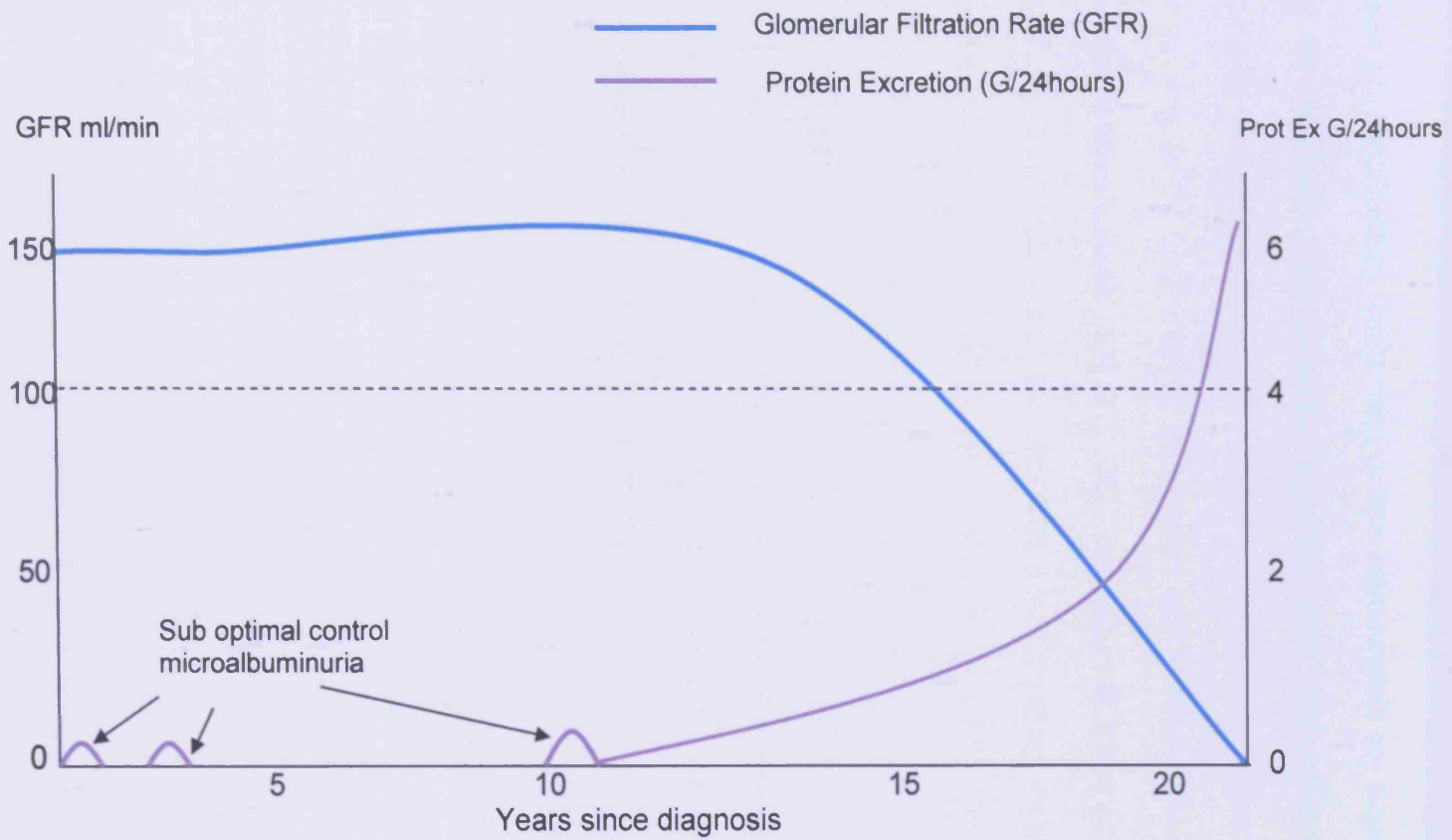
1.6.6 Lipids and the development of cardiovascular disease and nephropathy

Dyslipidaemia is part of the metabolic derangement present in Type 2 diabetes. There is a body of evidence that supports the hypothesis that links cardiovascular risk to elevated levels of serum lipids. In addition, it has now been documented that an elevated level of cholesterol is an identifiable factor in the loss of renal function [61]. The treatment of hyperlipidemia has a well-established role in reducing cardiovascular endpoints in patients with diabetes with most data being available for the statins. The Heart Protection Study included 5963 patients with diabetes who were prospectively randomized to treatment with simvastatin or placebo [62]. Active treatment was associated with a 27% reduction in coronary events. In the trial as a whole, the benefit of statin therapy for reducing cardiovascular risk was independent of the baseline low-density lipoprotein (LDL) cholesterol level. In the Collaborative Atorvastatin Diabetes Study, 2838 patients with type 2 diabetes age 40-75 years were randomized to placebo or treatment with atorvastatin 10 mg daily [63] Although the median duration of follow-up in this trial was short at 3.9 years, treatment with atorvastatin reduced acute coronary heart disease events by 36%, coronary revascularizations by 31%, stroke by 48%, and overall death rate by 27%. Other studies have reported similar benefits including that of Tonelli and colleagues [64] who reported that Pravastatin was of benefit in proteinuric renal disease .

1.7 Diabetic Nephropathy what is it?

The involvement of the kidney in the consequences of diabetes is characterised firstly by glomerular hyperfiltration without the presence of albumin in the urine or raised blood pressure. Between five to fifteen years post diabetes diagnosis a proportion of patients will excrete levels of albumin in their urine of between 30 to 300 milligrams in 24 hours (microalbuminuria). This 'incipient nephropathy' is allied to a normal Glomerular Filtration Rate (GFR). Within a variable time frame (usually 10 to 15 years post diagnosis), overt nephropathy develops and is illustrated in Figure 9. Overt nephropathy is characterised by increasing albumin excretion in the urine, increasing blood pressure and a decrease in GFR. Studies have shown that after ten years of follow up, the risk of diabetic nephropathy was 29 times greater in patients with Type 2 Diabetes Mellitus with urinary albumin excretion levels > 10μg/minute. Although microalbuminuria has been considered a risk factor for macro albuminuria, not all patients progress to this stage and it is believed that between 20-30% revert to a normoalbuminuria state, 40% progress to proteinuria and renal failure and 30% have persistent microalbuminuria.

Figure 9: Course of Diabetic Nephropathy



1.8 Association between cardiovascular disease and diabetic nephropathy

The development of nephropathy in patients with Type 2 diabetes, reflects vascular dysfunction elsewhere in the body. As described previously, albuminuria is the first clinical indicator of nephropathy and increases the risk of cardiovascular events independently of traditional risk factors [65] [66].

A number of comorbidities result from or are exacerbated by, damage to the kidney, for example hypertension, anaemia and dyslipidaemia. These comorbidities occur more frequently, earlier in the disease process and with greater severity in the nephropathy associated with diabetes than in kidney disease due to other causes [54] [67] [68]. The nature of these comorbidities mean that most individuals with diabetes who develop kidney disease will die from cardiovascular disease before they require dialysis [69]. Data from the Heart Outcomes Prevention Evaluation (HOPE) showed that the risk of major cardiovascular events in individuals, both with and without diabetes, increases at levels of albuminuria below the current threshold for microalbuminuria [70]. Studies have also shown that the risk of cardiovascular events rise with increasing levels of urinary albumin excretion [71]

The influence of kidney disease on cardiovascular disease is due to many interrelated factors for example; by the time the kidney is affected by vascular disease the disease process itself is severe and widespread in the body. Endothelial dysfunction, which is a component of atherosclerosis and occurs in the general circulation as well as the glomerular microcirculation, is

indicated by the presence of albuminuria. Individuals with Type 2 diabetes and albuminuria are at increased risk of cardiovascular disease [65] [66] .

1.9 Pathological changes in the kidney

Renal pathology has been less well studied in Type 2 patients than in Type 1 patients. There has been some controversy associated with reports that there is a high incidence of non diabetic renal lesions in biopsies from Type 2 diabetic patients [72], however it is felt that this may represent selection bias (more atypical cases) as this finding has not been replicated in other studies. There is no doubt that the lesions found in biopsies of Type 2 patients are more heterogeneous than those in Type 1 patients [73]. In general, it appears that a substantial proportion of type 2 patients have tubelo-interstitial disease and vascular injury which is out of proportion to their glomerulopathy [74]. On examination of renal biopsy, there is a consensus that the main findings are:

- Thickening of the glomerular basement membrane
- Renal Hypertrophy
- Mesangial matrix expansion
- Hyalinisation of arterioles.

The appearance of renal disease in patients with Type 2 diabetes may be due to other causes than diabetic nephropathy. The incidence of non diabetic renal disease in Type 2 patients has been reported to be as high as 30 percent but a review by Olsen et al [75] has suggested that the variability in the rate of non-diabetic disease may be due to selection bias.

1.10 Prevention

Clinical research studies have identified areas of diabetic care that can be used to modify the progression of patients with Type 2 diabetes to renal failure. Strategies have been developed which will be examined in more detail in subsequent chapters of this thesis but they can be broadly divided into three distinct areas.

1.10.1 Primary Prevention

Primary prevention is described as strategies applied to all diabetic patients, at risk of developing renal disease, to prevent the development of diabetic nephropathy. It has been demonstrated in Type 1 diabetes that intensive control of blood glucose levels reduce the proportion of patients developing diabetic nephropathy. The Diabetes Control and Complications Study [23] was designed to investigate whether Intensive Therapy (IT) when compared to Conventional Therapy (CT) would affect the risk of onset and progression of complications. The risks of the microvascular complications over the average of 6.5 years of follow-up were reduced by 26-63% with intensive versus conventional therapy. The IT group achieved a median HbA_{1C} throughout the study of 7.2% *vs.* 9.1% in the CT group ($p<0.001$). Early renal damage, the appearance of microalbuminuria (defined as AER > 40 mg/24 hours) was reduced by 60%. In addition, clinically significant renal damage, (defined as Albumin Excretion Rate (AER) of > 300 mg/24 hours) was reduced by 54%.

In patients with Type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) [21] reported a relative risk of 0.8 for the intensively controlled group when compared with those randomised to conventional control.

In addition, a study by Ravid et al demonstrated a decrease in urinary albumin with an ACE inhibitor and therefore, in the risk of development of diabetic nephropathy that was independent of any effect on blood pressure [76].

Recent studies have also suggested that lower is better in terms of blood pressure levels and confers increased benefit even when reduced into the normotensive range. Pohl and his colleagues have demonstrated that progressive lowering of systolic blood pressure to 120 mmHg was associated with improved renal and patient survival, an effect which was independent of baseline renal function. No relationship could be demonstrated in this study between diastolic blood pressure and renal outcomes [77]

1.10.2 Secondary Prevention

Secondary prevention is targeted at patients who already have microalbuminuria and aims to slow progression to overt nephropathy

Early treatment of hypertension is very important in diabetic patients both to prevent cardiovascular disease and to minimise progression of renal disease [78]. Amongst Type 2 diabetics, the benefit of strict blood pressure control

may be as great or greater than the benefit conferred by strict glycaemic control [21].

Since hypertension places diabetic patients at very high risk of cardiovascular complications, it has been recommended that all diabetics with blood pressures above 140/90 mmHg should start antihypertensive drug therapy immediately [79], [80]. The evidence is unequivocal that intensive drug therapy is protective [21], [78], [81] and therefore, all diabetics should have their blood pressure reduced to below 130/80 mm of mercury as detailed in recommendations adapted from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and illustrated in Figure 10 [82].

Figure 10: Classification and management of blood pressure for adults aged 18 years or older

Classification	Systolic (mm Hg)		Diastolic (mmHg)	Initial Drug Therapy	
				Without compelling indication	With compelling indication
Normal	<120	and	<80		
Prehypertension	120-139	or	80-89	No antihypertensive drug indicated	Drug(s) for the compelling indicationsΔ
Stage 1 hypertension	140-159	and	90-99	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, beta blocker, CCB, or combination	Drug(s) for the compelling indications; other anti-hypertensive drugs (diuretics, ACE inhibitor, ARB, beta blocker, CCB) as needed
Stage 2 hypertension	≥ 160	and	≥ 100	2-drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or beta blocker or CCB)◊	Drug(s) for the compelling indications; other antihypertensive drugs (diuretics, ACE inhibitor, ARB, beta blocker, CCB) as needed

ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker; BP: blood pressure; CCB: calcium channel blocker.

* Treatment determined by highest BP category.

ΔTreat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mmHg. Other compelling indications include disorders such as heart failure, post-myocardial infarction, and atrial fibrillation in which particular antihypertensive drugs are warranted independent of BP.

◊Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

Adapted from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, Hypertension 2003; 42, 1206-1252.

1.10.3 Tertiary Prevention

There is little evidence to suggest that patients who have developed overt nephropathy, benefit, in terms of disease progression, from tight glycaemic control in this stage of the disease process, although poor glycaemic control has been shown to be associated with progression and predict a poor outcome on dialysis. By contrast, modification of life style factors and drug therapy in the long term control of hypertension has been shown to delay progression of renal disease

1.10.3.1 Evidence underpinning choices of drug therapy in the management of hypertension in tertiary prevention.

Initial treatment plans should be tailored to lifestyle changes including weight reduction, introduction of healthy diet, exercise plans and smoking cessation. The choice of agents to control blood pressure is based upon their efficacy in two areas, firstly their ability to slow the progression of renal disease and secondly their ability to prevent cardiovascular morbidity and mortality. There is extensive evidence of the effect of both Angiotensin Converting Enzyme (ACEi) inhibitors and Angiotensin Receptor Blocker (ARB) in slowing the progression of renal disease and although this will be dealt with in some depth in Chapter 4, it is important to highlight the main evidence.

Much of the information available on the potential of ACE inhibitors to slow the progression of nephropathy has been carried out in Type 1 Diabetes Mellitus

although the small number of studies in Type 2 diabetes appear to show a similar effect. Currently more data are available in Type 2 diabetes on the effect of ARBs. In the Irbesartan Diabetic Nephropathy trial, over 1700 patients with type 2 diabetes and hypertension and nephropathy were assigned randomly to treatment and the results showed a reduction for the patients on an ARB of 23 (versus amlodipine) and 20 per cent (versus placebo) in the combined endpoint of (doubling in serum creatinine, all cause mortality and cardiovascular events). The study also showed a threshold of 120mg Hg for the decrease in cardiovascular death and heart failure and doubling of serum creatinine or progression to end stage renal disease. [77, 83] ,

In clinical practice, therapy is normally initiated with an ACE inhibitor or an ARB. This is largely based upon the evidence that such agents protect against the development of progressive nephropathy. If the blood pressure is not controlled by an ACEi or ARB alone the addition of a diuretic is recommended. A thiazide is added if the goal blood pressure is not attained with an ACEi/ARB alone which has been administered at the maximally recommended dose.

The K/DOQI clinical practice guidelines recommend that the goal for blood pressure for patients with reduced renal function should be to 130/80 mmHg, [84]. There is evidence suggesting that an even lower systolic pressure may be more effective in slowing progressive renal disease in patients with a spot urine total protein-to-creatinine ratio ≥1000 mg/g [85].

As described in this chapter, the basis for modification of the progression of diabetic nephropathy and lowering of cardiovascular risk should be centered on treatment of known and modifiable risk factors for both comorbidities. In this thesis, the focus of study will encompass the

- Accurate and timely screening for the presence of microalbuminuria, as identification underpins the required interventions.
- Treatment and management of blood pressure
- Investigation of the potential genesis of anaemia in diabetic nephropathy given the precipitous reported nature of the development of anaemia in diabetic nephropathy and the effect of anaemia in left ventricular hypertrophy and increased cardiovascular risk.

Chapter 2

Methods

2. Study profiles

Three studies in diabetic nephropathy comprise the totality of this thesis;

a) Study 1, in two parts, undertook screening and assessment of Diabetic Nephropathy in the Diabetic Clinic,

b) Study 2 – Optimisation of risk factor management of the patient cohort identified in Study 1, for 12 months *and*

c) Study 3 – An exploration of haematolological and haematinic parameters in a selected subgroup of the original cohort.

2.1 Study One

2.1.1 Screening of patients with Diabetic Nephropathy in the Diabetic Clinic

All patients enrolled into Study 1 attended the diabetic clinic led by a single diabetologist based at a teaching hospital. Patients in the initial phase comprised all consecutive patients seen in the diabetic clinic over a 6month period. Data (patient notes and laboratory records) from this initial patient cohort were evaluated to ascertain the number of patients with diabetic nephropathy and whether this diagnosis was available to the physician at clinic attendance. The diagnosis of diabetic nephropathy used by the clinic prior to any intervention used a standard screening protocol based on the formal quantification of microalbuminuria on three separate occasions.

Incipient nephropathy was defined as persistent microalbuminuria ranging from 20-200mg/l hours in at least three consecutive urinary samples. Overt nephropathy was defined as albuminuria greater than 200mg/24h. Patients with impaired renal function in the absence of proteinuria, patients with microscopic haematuria and patients with known multi-system disease were excluded from this study.

2.1.2: Assessment of patients with Diabetic Nephropathy in the Diabetic Clinic by a dedicated nurse specialist

In the second phase of this part of the study, screening for diabetic nephropathy was co-ordinated and performed by a newly appointed dedicated nurse specialist who altered the method for screening. Prospective quantification of albumin: creatinine ratio on a random single urine sample collected at the time of the clinic visit prior to seeing the physician, using a CLINITEK 50 Analyzer (Bayer Corporation, Elkart, U.S.A.) was carried out for an 8 month period. In all patients with elevated albumin: creatinine ratios (men>2.5mg/mmol, women >3.5mg/mmol), subsequently albuminuria was confirmed by timed urine collection following a discussion with the nurse specialist regarding the probable diagnosis and the benefit of early identification and treatment.

Out-patient patient assessment included demographic data, serum creatinine, HbA_{1c}, and cholesterol (Figure 11). Blood pressure was measured with an calibrated automatic digital blood pressure monitor, after 5-10 min sitting at the clinic using an algorithm (Figure 12) to aid decision making. Where necessary, ambulatory Blood Pressure was measured using Spacelabs ambulatory blood pressure system In addition prescribed medication was assessed and in particular the use of Angiotensin Converting Enzyme inhibitors, Angiotensin Receptor Blockers, aspirin and cholesterol lowering medication noted.

2.2 Study 2: Optimisation of risk factor management during twelve month follow up of cohort identified in Study 1

Study Two consisted of follow up of a patient cohort with diabetic nephropathy who had their management optimised over a twelve month period and treatment intervention instigated and recorded by a dedicated nurse specialist using both primary and secondary care to effect and maximise change.

Clinic blood pressure was measured with an automated digital blood pressure monitor (Omron Healthcare UK, Henfield, West Sussex, UK) after a 5-minute seated rest. An algorithm was designed to assist and standardise the identification of all patients with sub optimally controlled blood pressure (Figure 12). The nurse then ensured that all clinic medical staff were informed that these patients needed treatment modification and made suggestions on optimal treatment using evidence based algorithms (Figures 13 and 14).

All patients with diabetic nephropathy (microalbuminuria) and blood pressure recordings at or below target had their drug treatment scrutinised by the specialist nurse to ensure ACEi and /or ARBs were being prescribed, even in the absence of hypertension. An algorithm was used for commencing ACE inhibition in normotensive nephropaths, not already prescribed these drugs, to ensure renal function and blood pressure were monitored appropriately (Figure 13).

A treatment intensification algorithm was provided for the nurse specialist to use for patients with diabetic nephropathy and blood pressure recordings above target (Figure 14). This was designed to maximise the use of ACE inhibitors and/or ARBs as first line management, with the addition of

Indapamide to act synergistically if blood pressure was not optimally controlled. Although the intensification policy is similar to that suggested by the British Hypertension Society published guidelines it is more prescriptive taking account of the high co-morbidity rates associated with a diabetic patient population.

Follow up

All patients with blood pressure measurement at or below target were allocated to routine follow up care comprising annual follow up in the diabetic clinic.

For patients above target, where possible, treatment changes were initiated in the diabetic clinic. However, in patients where this was not possible, the link between the nurse specialist and the Primary Care team was utilised to bring about treatment change.

In addition to the Clinical Nurse Specialist and the Primary Care Team, a Consultant Nephrologist was available to offer additional advice about treatment changes or difficult management decisions. Follow up was arranged with primary care and information from the follow up visits was fed-back to the Clinic Specialist Nurse. Once blood pressure was at target the patients were then seen 3 monthly by the Practice Nurse.

2.3 Study 3: Development of anaemia in individuals with type 2 Diabetes Mellitus

In this study on the development of anaemia, a sub group of individuals were identified from the Research Clinic of the Academic Diabetes Research Unit, Llandough Hospital, Cardiff, where they were under long term follow up. All patients had been followed up for a minimum of five years. Sixty two (62) patients gave written informed consent. All recruited patients had Type 2 diabetes and had undergone exhaustive yearly health checks, including formal isotope measurement of Glomerular Filtration Rate (GFR) and assessment of proteinuria.

Data collection was undertaken both prospectively during annual review and retrospectively from a search of medical records and electronic patient haematology results.

For research purposes serum ferritin, serum erythropoietin levels and reticulocytes were measured at annual diabetic review, in addition to routine parameters including haemoglobin, haematocrit, HbA_{1c}, and Glomerular Filtratation Rate. In addition retrospective haematological results were collected from the patient records, for the period prior to recruitment in order to examine the effect of time since diabetes diagnosis on haematological parameters.

2.4 Statistical Analysis

Statistical analysis was undertaken using SPSS for Windows Version 14.0. All parameters were tested for distribution and as appropriate, parametric and non parametric analyses were undertaken.

For variables with normal distribution, values were reported as Mean ± (Standard Error of Mean) and analysed using paired or unpaired T-tests as appropriate. For variables which were not normally distributed, values were reported as median (Inter Quartile Range) and non parametric statistical analysis were used, including Kruskal Wallis tests for k independent variables and Mann-Whitney tests for two independent variables. Where appropriate, Chi-squared analysis was undertaken. The criterion for statistical significance in all cases was $p<0.05$.

Graphical representation of all continuous variables were made using 'box and whisker' plots with the upper and lower limits of each box representing the 75^{th} and 25^{th} centile respectively and the line within the box indicating the median value. The lowest and highest values in each case were represented by the 'whiskers'. Outliers, (values greater than two standard deviations from the mean) were represented by open circles and extremes (values greater than three standard deviations form the mean) by an asterisk.

In addition, histograms and frequency charts were used, where appropriate, including a 'normal curve'.

Figure 11: Diabetic Nephropathy - Screening

Addressograph Label

Date			
Weight			
BMI			
Diabetes Treatment			
HbA1C			
Blood Glucose			
Systolic			
Diastolic			
Anti Hypertensives			
MA1			
MA2			
MA3			
Proteinuria			
Urinary Protein			
Creat Clearance			
Cholesterol			
Trigs			
HDL			
LDL			
Ratio			
Statins			
Urea			
Creatinine			
Hb			
Ferritin			
Other medication			
Action/Comments			

Figure 12

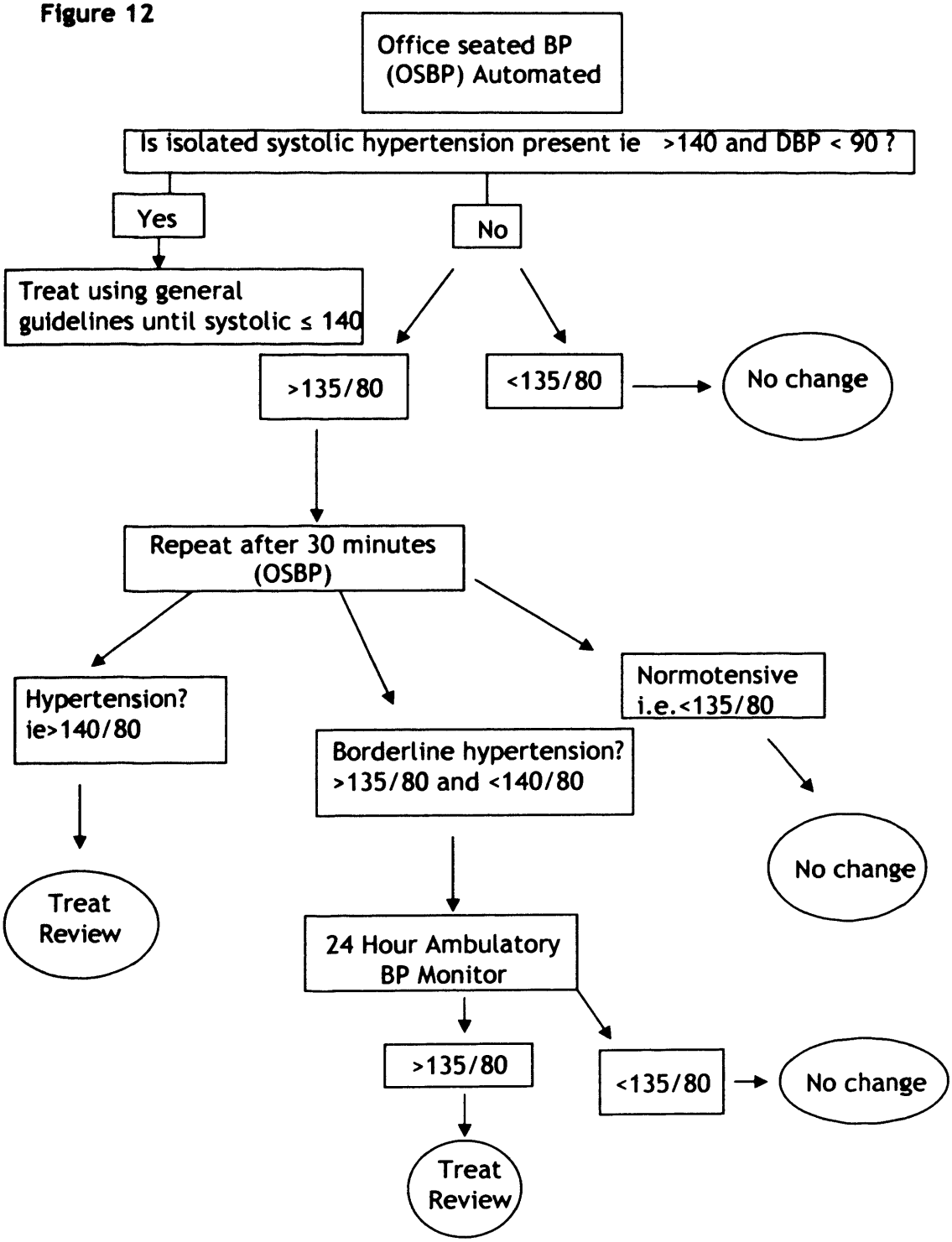

Office seated BP (OSBP) Automated
Is isolated systolic hypertension present ie >140 and DBP < 90 ?
Yes
No
Treat using general guidelines until systolic ≤ 140
>135/80
<135/80
No change
Repeat after 30 minutes (OSBP)
Hypertension? ie>140/80
Borderline hypertension? >135/80 and <140/80
Normotensive i.e.<135/80
No change
Treat Review
24 Hour Ambulatory BP Monitor
>135/80
<135/80
No change
Treat Review

Figure 13

ACE inhibitors and normotensive nephropaths

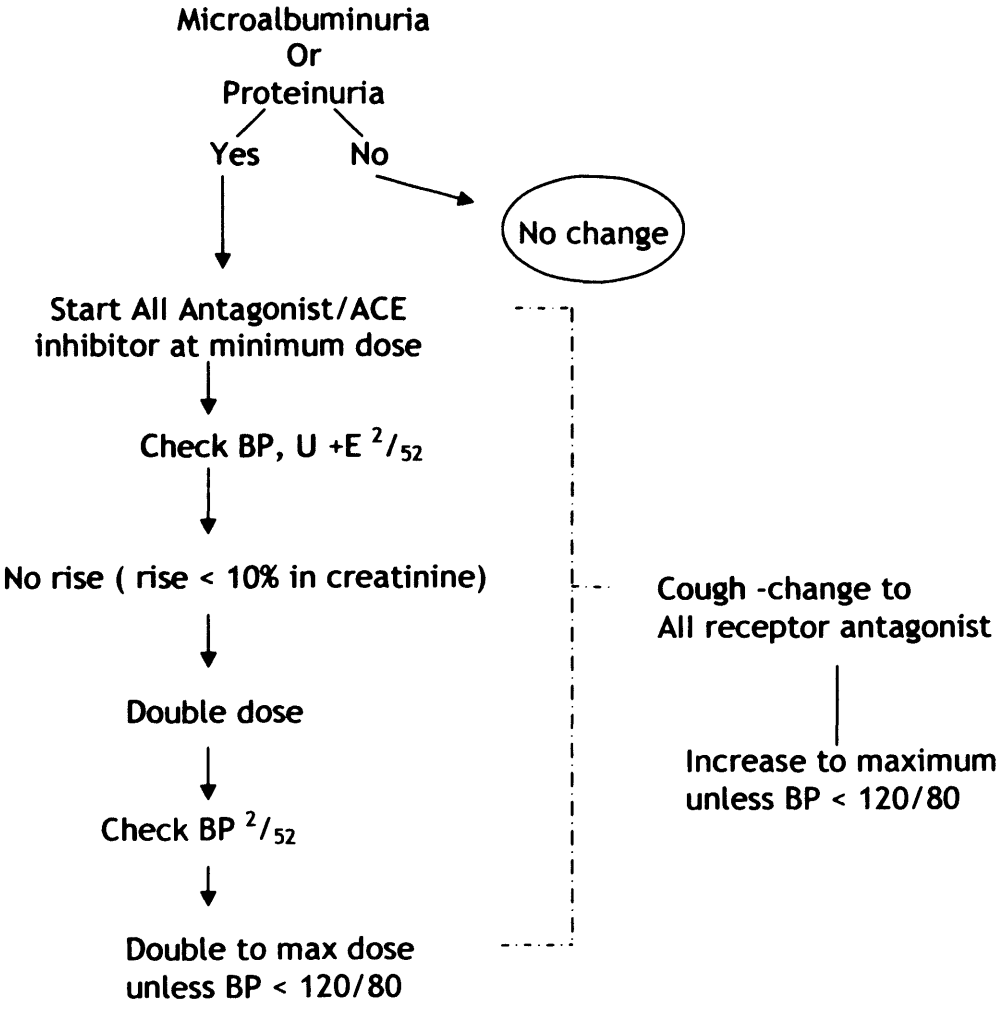
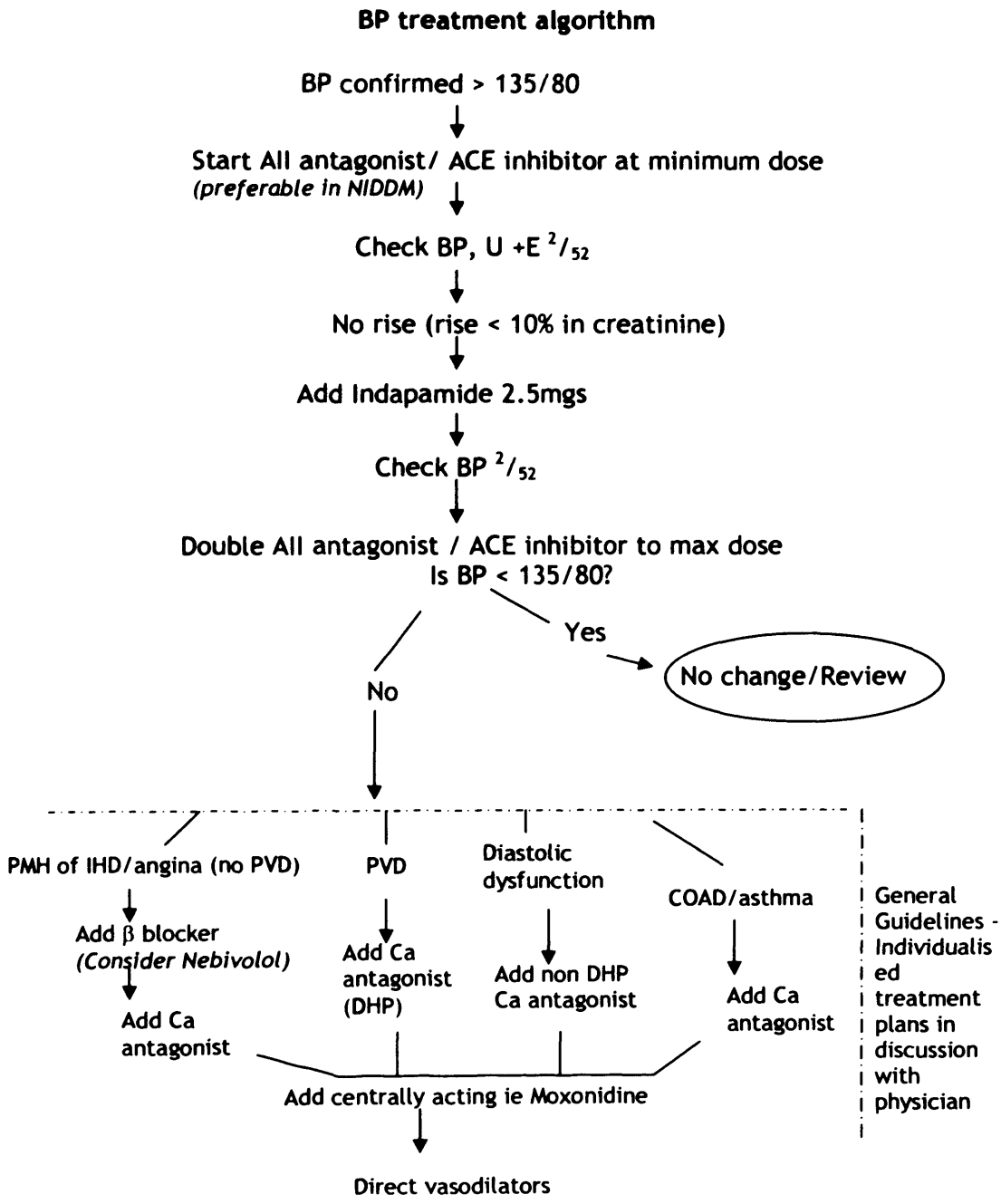


Figure14


BP treatment algorithm
BP confirmed > 135/80
Start All antagonist/ ACE inhibitor at minimum dose
(preferable in NIDDM)
Check BP, U +E 2/52
No rise (rise < 10% in creatinine)
Add Indapamide 2.5mgs
Check BP 2/52
Double All antagonist / ACE inhibitor to max dose
Is BP < 135/80?
Yes
No change/Review
No
PMH of IHD/angina (no PVD)
PVD
Diastolic dysfunction
COAD/asthma
Add β blocker
(Consider Nebivolol)
Add Ca antagonist
Add Ca antagonist (DHP)
Add non DHP Ca antagonist
Add Ca antagonist
Add centrally acting ie Moxonidine
Direct vasodilators
General Guidelines - Individualised treatment plans in discussion with physician

Chapter 3

Identification and Management of Diabetic Nephropathy in the Diabetic Clinic

3.1 Introduction

Studies performed to date focusing on referral patterns and management of diabetic nephropathy in nephrology clinics have highlighted sub-optimal care and late referral [86], [87]. It is clear however, that appropriate implementation of treatment guidelines following referral to specialised clinics, either diabetic-renal clinics [86] or nephrology clinics [87] , slowed the progression of established diabetic nephropathy. The importance of early referral and intervention is also apparent since a retardation in the rate of decline in renal function may take up to 3 years [86]. It has also been shown that implementation of a multi-factorial approach to the diabetic patient leads to improvement in progression of complications other than nephropathy [78]

As highlighted in preceding chapters, for the majority of patients, screening is not merely undertaken to detect progressive renal disease. Only thirty to forty percent of diabetic patients will develop microalbuminuria and of those around forty percent will develop proteinuria which may progress to renal failure. For those without microalbuminuria, detection and modification of cardiovascular risk will be the most important factor in patient management. During an eight year follow-up study in Norway, only 38 of the 3069 people with chronic kidney disease with and without diabetes progressed to end stage renal disease. In contrast, there was a high cardiovascular mortality: 3.5, 7.4, and 10.1 deaths per 100 person years among people with a glomerular filtration rate 45-59, 30-44, and <30 ml/min/1.73 m^2, respectively In this study, Hallan et al concluded from this that screening individuals with hypertension, diabetes mellitus, or age >55 years was the most effective strategy for the

detection of patients with chronic kidney disease, but the risk of end stage renal disease among those detected was low [88].

In a recent study amongst Chinese patients, researchers found that Chinese type 2 diabetic patients with reduced eGFR were at high risk of developing cardiovascular end points and all-cause mortality, independent of albuminuria and metabolic control. [89]

Patients with diabetic nephropathy and reduced GFR require long term follow up and management and the effect of age has been underlined in a recent study undertaken by O'Hare and colleagues, which highlights the effect of age on the relationship between glomerular filtration rate and mortality [90]. Evidence from the PROGRESS study demonstrates the effect of reduction of cardiovascular risk (by lowering blood pressure) on the recurrence of cerebrovascular events [91].

Maximal reduction in the morbidity and mortality of patients with diabetic nephropathy requires early identification of 'at risk' individuals allowing instigation of appropriate management protocols known to influence renal and cardiac outcome.

In the current chapter, assessment has been carried out on the efficiency of current practice in early identification and management of diabetic nephropathy in terms of both renal and cardiovascular risk. In addition, examination has been undertaken of the impact of changing screening procedures and the identification of the 'true at risk' population.

3.2 Results

3.2.1 Identification of patients with Diabetic Nephropathy in the Diabetic Clinic.

The initial phase of the study was used to delineate current practice, assess screening rates and make decisions on improvements to screening and management for renal and cardiovascular risk that could be undertaken in this patient group.

3.2.1.1 Definitions of nephropathy

Incipient nephropathy was defined as persistent microalbuminuria ranging from 20-200 milligrams (mg) per litre in twenty four hours in at least three consecutive urinary samples. Overt nephropathy was defined as albuminuria greater than 200mg/24hours. Patients with impaired renal function in the absence of proteinuria, patients with microscopic haematuria and patients with known multi-system disease were excluded.

3.2.1.2 Current Practice

Current practice within the diabetic clinic included blood pressure measurement and microalbumin screening at diagnosis and at yearly intervals. Results were reported to Primary Care after this appointment but no joint management plan for each patient was put in place and no agreed targets for blood pressure or re-referral to the specialist clinic were formally identified.

The screening for and measurement of microalbuminuria was particularly problematic and complex. All patients were given three (3) containers for

collection of early morning urine samples, which were then returned to their General Practitioner who arranged for the samples to be sent for analysis. Once results were received, they were copied and sent to the specialist diabetic clinic were it was planned that all results were filed in the patient medical notes.

3.2.1.3 Demographics of Patient Cohort

In the initial patient cohort, a total of six hundred and forty four (644) patient notes and laboratory records were evaluated. Microalbuminuria results were available for four hundred and eighty five (485) patients (75%). Of these, 115 patients were identified as meeting the criteria for a diagnosis of diabetic nephropathy giving an observed prevalence of diabetic nephropathy of 17%. The overwhelming majority of these (90.6%) were type 2 diabetics. Demographic data for the identified nephropaths is shown in Table 1. Of those patients identified with diabetic nephropathy, 72.6% had incipient nephropathy, 27.4% had overt nephropathy and of the latter group 78.6% had elevated serum creatinine levels. The mean serum creatinine for incipient and overt nephropathy group was 91(76-145) µmol/l, median (IQR) and 112 (109-141)) µmol/l, median (IQR) respectively.

Of the 115 known patients with nephropathy, results of urinary microalbumin or proteinuria quantification were available for the physician at the time of the out-patient consultation in only 53% of the patient case records. The remaining patients with nephropathy could only be identified from the patients' laboratory records and were not available to the physician at the time of consultation.

Due to resource constraints, it was not possible to undertake a more detailed review of the patient characteristics of the group but the fact that only half of the patients had microalbumin screening results available at the time of physician review gave cause for concern.

The process surrounding the original screening at diabetic clinic was cumbersome and even with very good patient compliance could take a considerable length of time. It involved the patient attending the diabetic clinic for review and being given three sample bottles to collect three consecutive early morning urine samples whilst they were there. The samples had to be delivered, by the patient, to their Primary Care surgery who would then send the samples on to the laboratory for testing. Results would then be returned to the surgery that might or might not forward the result to the diabetic clinic. Patients sent their samples at varying times, post appointment, some not remembering until they were due to attend for their follow up appointment 12 months later. Positive review of returned microalbumin results was undertaken by the administrative staff of the specialist centre who ensured that results were reviewed by a consultant but there was no formalised system of follow up for those who did not return their samples.

3.2.2 Assessment of management of patients with diabetic nephropathy in the Diabetic Clinic

From the initial study, twenty five (25) percent of patients were not screened and of those that were screened, forty seven (47) percent of results were not available at the time of physician consultation. In the second phase of the study, screening for diabetic nephropathy was co-ordinated and performed by a newly appointed dedicated nurse specialist. Previous studies have demonstrated the efficacy of quantification of the ratio of urinary albumin to creatinine in a random single voided urine sample as a reproducible alternative to the formal quantification of urinary protein loss [92]. In addition to appointment of the nurse specialist, during the second phase of the study, screening practice for diabetic nephropathy was altered. Prospective quantification of albumin: creatinine ratio on a random single urine sample collected at the time of the clinic visit prior to seeing the physician, using a CLINITEK 50 Analyzer was carried out on patients attending the diabetic clinic over a further eight (8) month period. In all patients with elevated albumin to creatinine ratios, albuminuria was confirmed by formal quantification following a discussion between the nurse specialist and the patient regarding the probable diagnosis and the benefits of early identification and treatment.

For all patients, at the time of out-patient visit, assessment included demographic data, serum creatinine, HbA_{1c}, cholesterol, haemoglobin and ferritin. Blood pressure measurement was standardised using an automated digital blood pressure monitor after five to ten minutes sitting at the clinic. In addition, prescribed medication was assessed and in particular the use of

Angiotensin Enzyme Converting Enzyme inhibitors, AII receptor antagonists, aspirin and cholesterol lowering medication noted.

The role of the dedicated nurse was extended to ensure that compliance with formal quantification of microalbumin levels in those who were positive on sampling was thorough and achieved total compliance of one hundred (100) percent.

In this patient cohort, 174 patients were identified as having diabetic nephropathy giving a prevalence of nephropathy of 20%, suggesting that prospective screening increased the number of diabetic nephropaths in the clinic population by 17.6%. Of these 174 patients, 134 had been identified previously as having diabetic nephropathy, by the existing screening practice, on the basis of positive urine albumin quantification. This was recorded either in the patients' records or in the laboratory records. Forty (40) patients however had no previous record of microalbumin quantification, and were therefore newly identified as having diabetic nephropathy from prospective screening.

Comparison of the demographic data of the known diabetic nephropathy patients identified in Phase I and those in Phase II revealed no differences in patient characteristics (Table 2) (age, sex, duration of diabetes, HbA_{1c}, Type1 vs. Type II, incipient vs. overt nephropathy).

Table 2: Characteristics of patients identified by standard screening in both the retrospective and prospective cohorts

	Phase I- known nephropaths n=115	Phase II- known nephropaths n=134
Age (years)	65 (55-71)	66 (58-72)
Gender (male:female)	62.1%:37.9%	63%:37%
% Type 2 diabetes	90.6%	95.1%
HbA_{1c} (units)	8.0 (7-9.7)	8.2 (7.1-9.4)
Duration of diabetes (months)	108 (60-192)	84 (48-156)
Incipient nephropathy	72.6%	75.9%
Overt nephropathy	27.4%	24.1%
Raised serum creatinine in those with overt nephropathy	78.6%%	50.0%

The prevalence of known patients with diabetic nephropathy in the retrospective and prospective cohorts was equivalent at 16.9% and 15.5 % respectively. The addition of the previously unknown patient cohort added an additional 4% giving a true prevalence of 19.5% as illustrated in Figure 15. As illustrated in Figure 16, the characteristics of patients in all three groups in terms of the proportion of Type 2 diabetics and the prevalence of overt nephropathy were similar.

Figure 15: Presumed and true prevalence of diabetic nephropathy

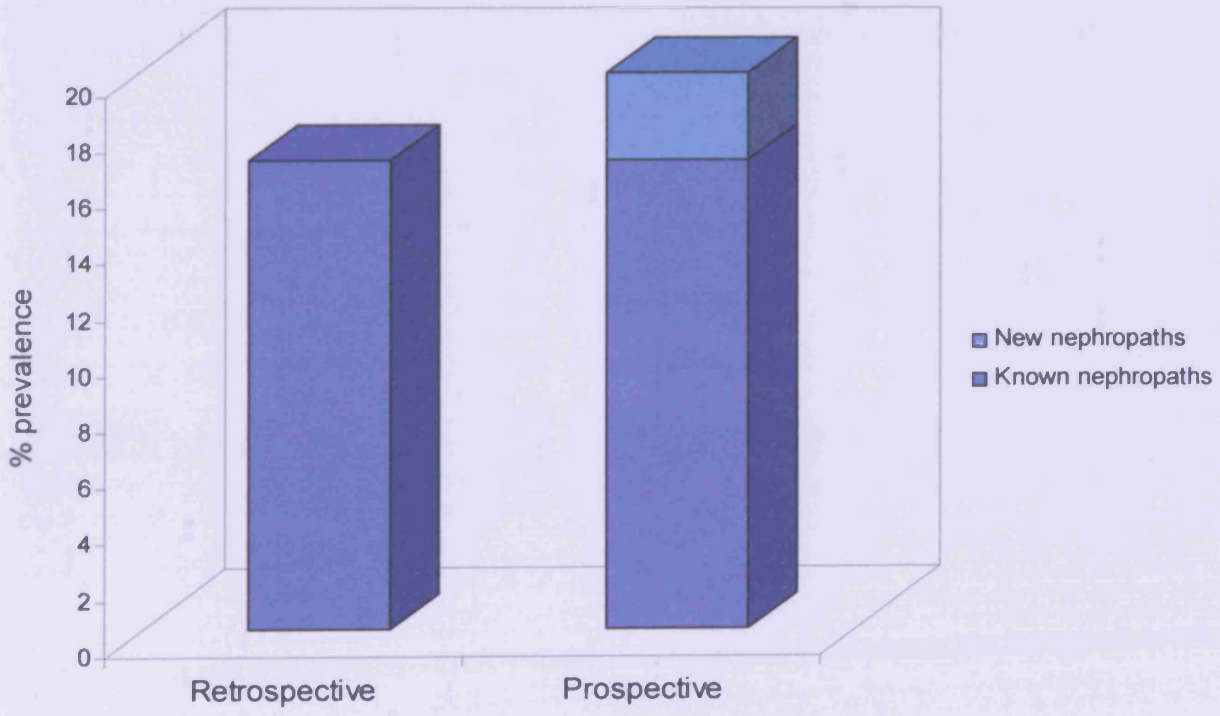
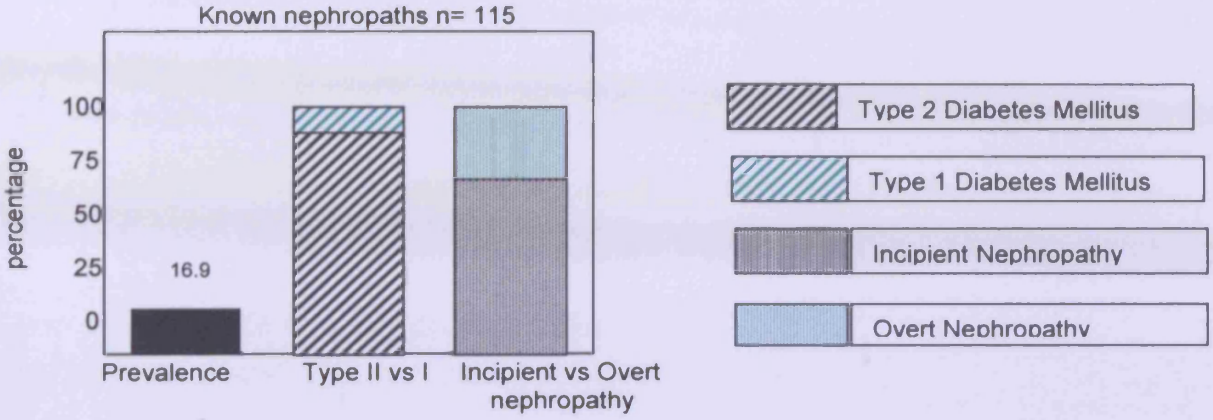
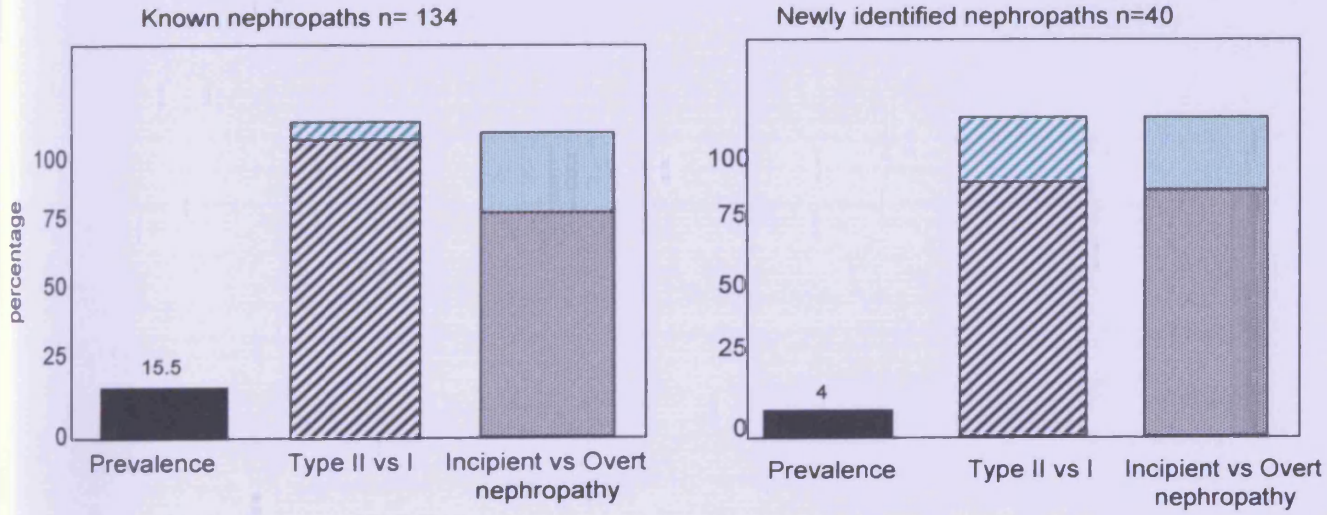


Figure 16: Comparison of background characteristics of patient groups

16.1 Retrospective patient group – 75% screening



16.2 Prospective patient group – 100% screening



Comparison of patient characteristics of all the known patients with nephropathy and those newly identified in Phase II is shown in Table 3. The serum creatinine for incipient and overt nephropathy in the newly identified group were 105 (87-162) µmol/l, median (IQR), and 102(83-159) µmol/l, median (IQR), respectively. There was no difference in age, sex, HbA_{1c}, duration of diabetes or incidence of incipient versus overt nephropathy. These data would suggest that these patients represent a cohort of patients truly missed by the standard practice in this clinic.

Table 3: Patient characteristics of diabetic nephropaths identified by standard screening and those newly identified nephropaths identified by nurse led prospective screening based on random measurement of urinary albumin to creatinine ratios.

	All known nephropaths n=249	Newly identified nephropaths n=40
Age (years)	66 (58-73)	66 (58-75)
Sex (male:female)	37.5% : 62.5%	45.7% : 54.3%
% type II diabetes	93.3%	80.%
Hba_{1c}	8.0 (7.0-9.5)	8.5 (7.8-10.2)
Duration of diabetes (months)	90 (60-168)	120 (48-180)
Incipient nephropathy	74.%	77.4%
Overt nephropathy	25.5%	22.6%
Overt nephropathy and raised serum creatinine	65.4%	50%

3.3 Risk factor management in known and newly identified nephropaths

Having identified a cohort of patients with diabetic nephropathy, the management of this patient group was examined and compared with the recommendations enshrined in the National Institute of Clinical Excellence guidelines for the management of renal disease in diabetes and outlined in Table 4 [93]

Table 4: NICE Guidelines: Renal care for all people with type 2 diabetes

The NICE guidelines, published in 2002 and due for review in 2005 (in progress) state that

Recall and annual review for people with type 2 diabetes.

Review complications and risk factors at diagnosis and at least annually

Measure urinary albumin: creatinine ratio or albumin concentration annually.

– Use a first morning urine sample where practicable and a laboratory or near-patient test specifically for microalbuminuria.

If microalbuminuria or proteinuria is present, repeat twice more (within 1 month where possible).

Measure serum creatinine annually and classify as: lower risk (absence of microalbuminuria or proteinuria), or higher risk.

Care for people with lower-risk albumin excretion

• Maintain good blood glucose control (preferably HbA1c below 6.5–7.5%, according to the individual's target)

• Maintain good blood pressure control (target blood pressure at or below 140/80 mmHg).

Care for people with higher-risk urine albumin excretion

If retinopathy is not present, look for a non-diabetes-related cause of renal disease (full history and examination, urinalysis, renal ultrasound, other investigations as appropriate)

Ensure good blood glucose control (HbA1c below 6.5–7.5%, according to the individual's target).

Measure, assess and manage cardiovascular risk factors aggressively including the maintenance of blood pressure below 135/75 mmHg Begin therapy with an appropriate ACE inhibitor for cardiovascular/renal protection. Combination therapy is likely to be necessary for most patients.

Measure urine albumin and serum creatinine levels at each visit.

Refer for specialist/nephrological opinion if serum creatinine greater than 150 μmol/l

3.4 Blood pressure control

Overall levels of systolic and diastolic pressure in the total identified cohort of patients with diabetic nephropathy are illustrated in Figures 17 and 18.

The number of patients with systolic blood pressure levels at or below target was 66 or 27.6 % of the total population. The distribution of systolic blood pressure levels, median (Inter Quartile Range) were 128 (120-130) mmHg in the group at target and 155.5(142-173.5) mmHg in those who were not at target and are illustrated in Figure 19.

The number of patients with diastolic blood pressure levels at or below target was 82 or 34.3% of total. Similar differences are seen in the levels (Median (IQR)) of diastolic blood pressure in those at target 68(62-71) mmHg and not at target 83(80-90) mmHg and are illustrated in Figure 20.

Figure 17: Systolic Blood Pressure

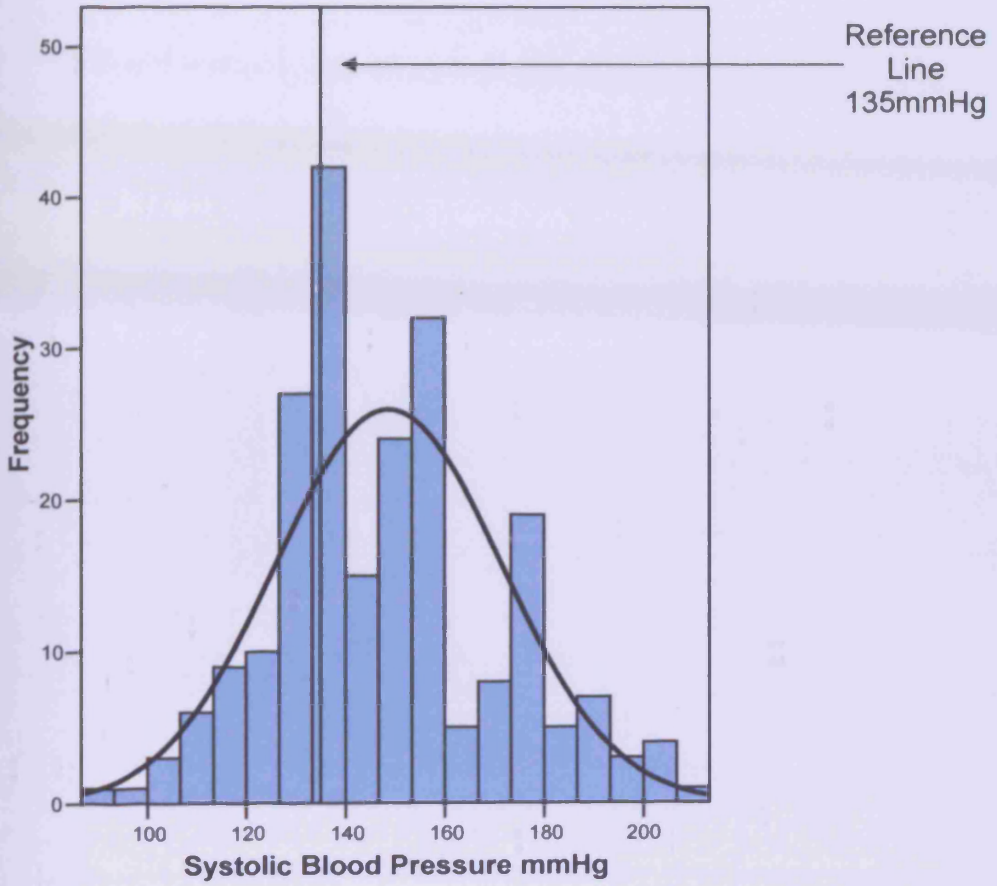


Figure 18: Histogram of Diastolic Blood Pressure

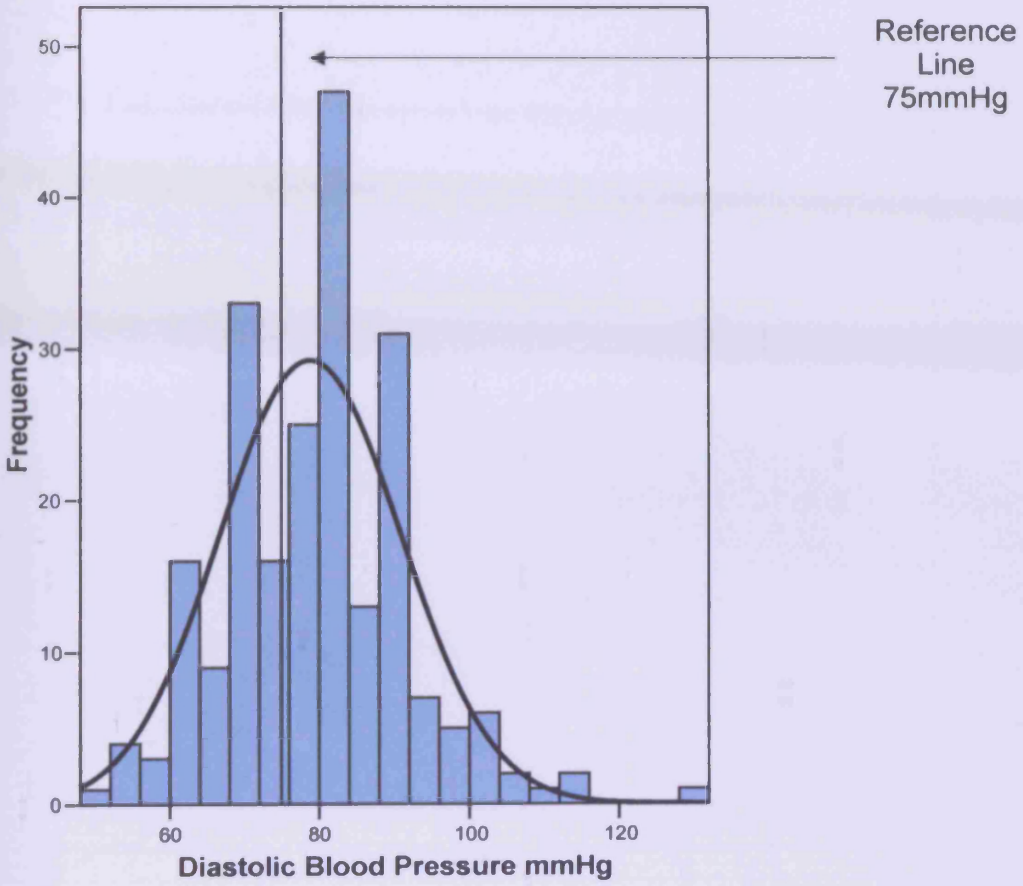


Figure 19: Systolic Blood Pressure levels of those at target and not at target

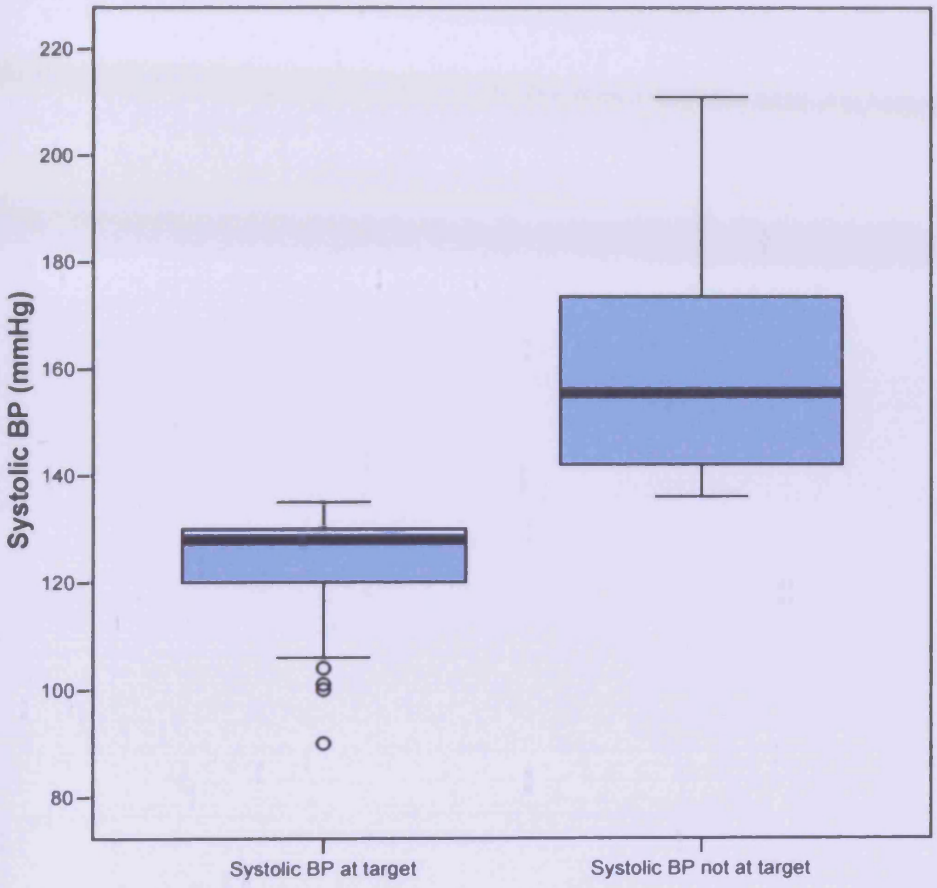
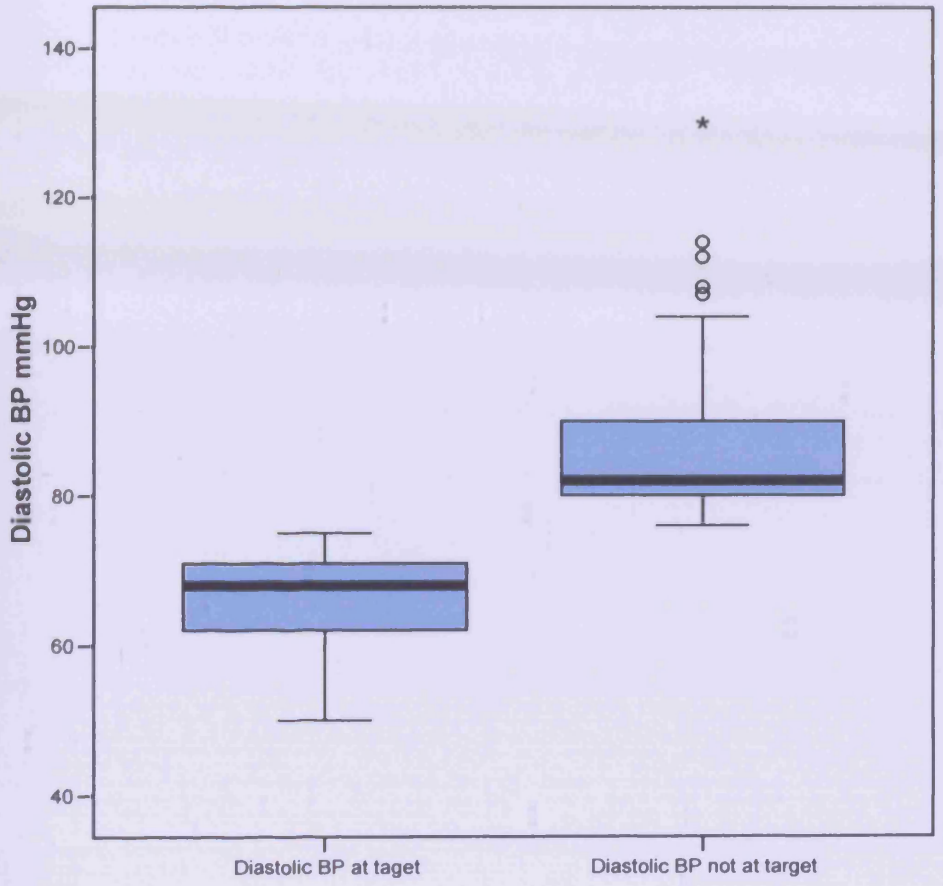


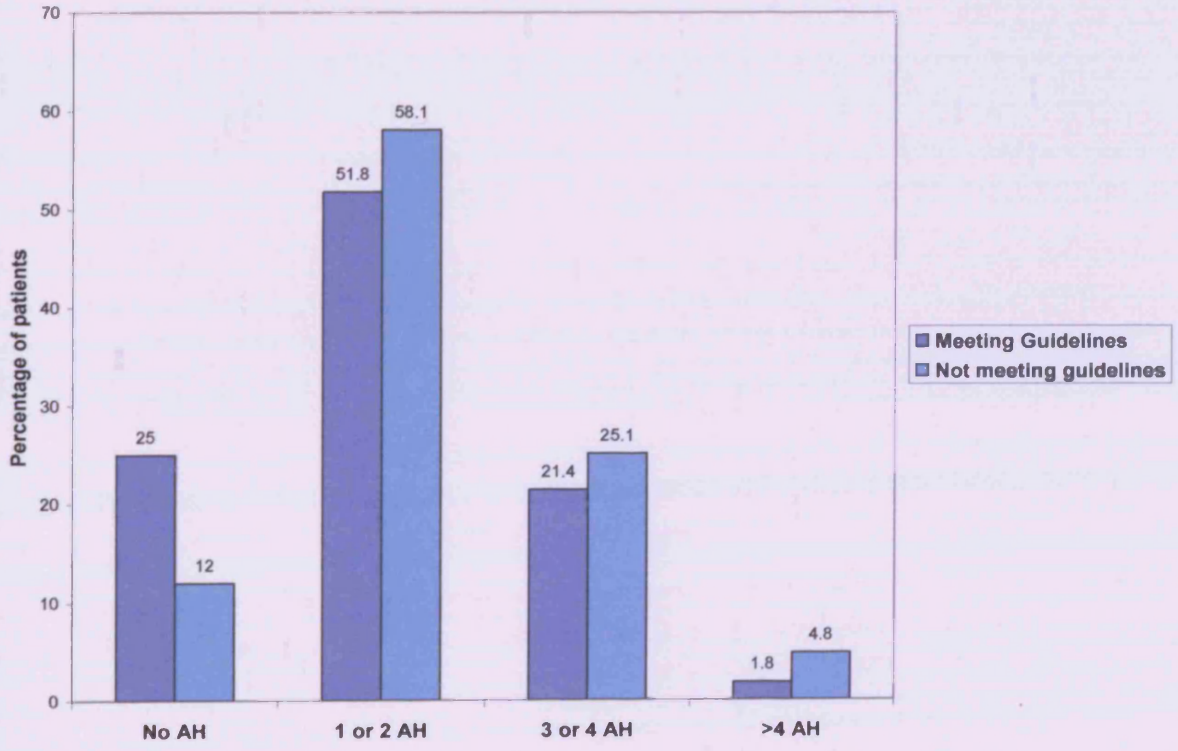
Figure 20: Diastolic Blood Pressure levels of those at target and not at target



Number of Prescribed Antihypertensive Agents

The number of antihypertensive agents that each patient had been prescribed was noted including Angiotensin Converting Enzyme Inhibitors (ACEI); Angiotensin Receptor Blockers (ARB); Calcium Channel Blockers; Beta Blockers; Centrally Acting Drugs; Diuretics and the total number of antihypertensive medications were counted and are shown graphically in Figure 21. As can be seen, there were numbers of patients meeting and not meeting targets for blood pressure who were and were not prescribed antihypertensive agents. No statistically significant difference could be demonstrated between those meeting and not meeting guidelines in terms of the number of prescribed antihypertensives.

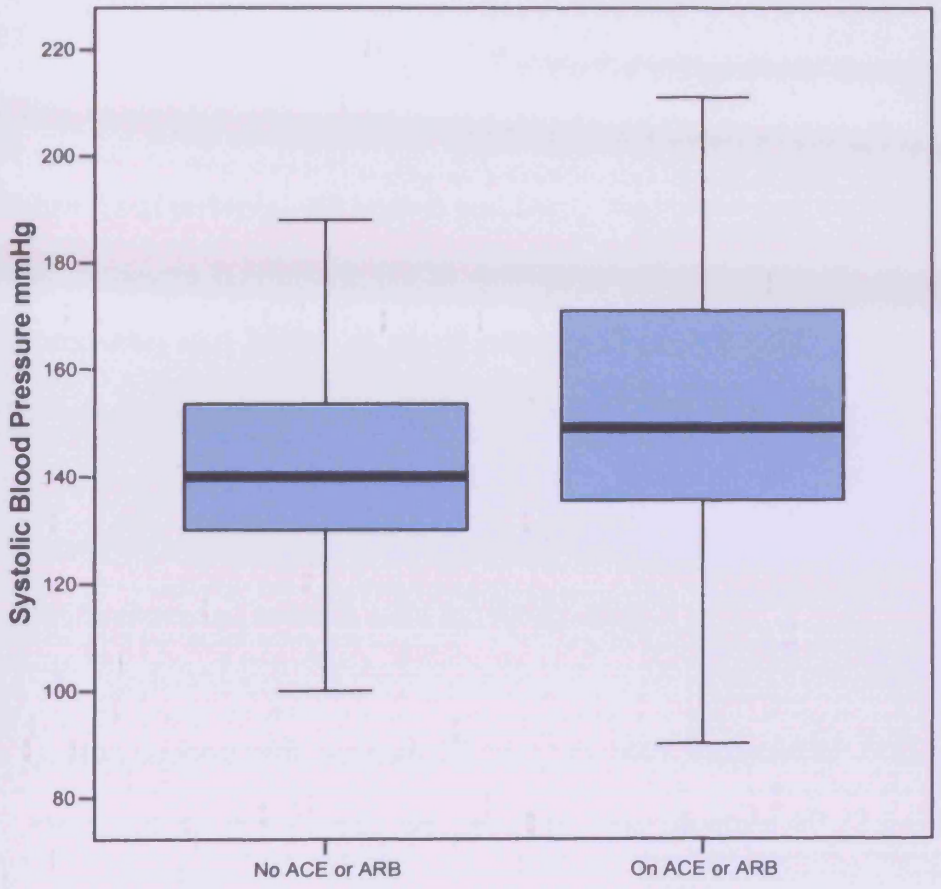
Figure 21: Total number of AntiHypertensive agents (AH) prescribed



Systolic Blood Pressure in those who were and were not prescribed ACEi and/or ARBs

The difference in systolic blood pressure levels in those who were and were not prescribed ACEI-Inhibitors or AR-Blockers are illustrated in Figure 22 and showed a statistically significant difference, p=0.003, using Mann-Whitney test. No difference could be demonstrated between diastolic blood pressure levels.

Figure 22: Systolic Blood Pressure of those not on treatment with ACEi or ARB compared with those on treatment

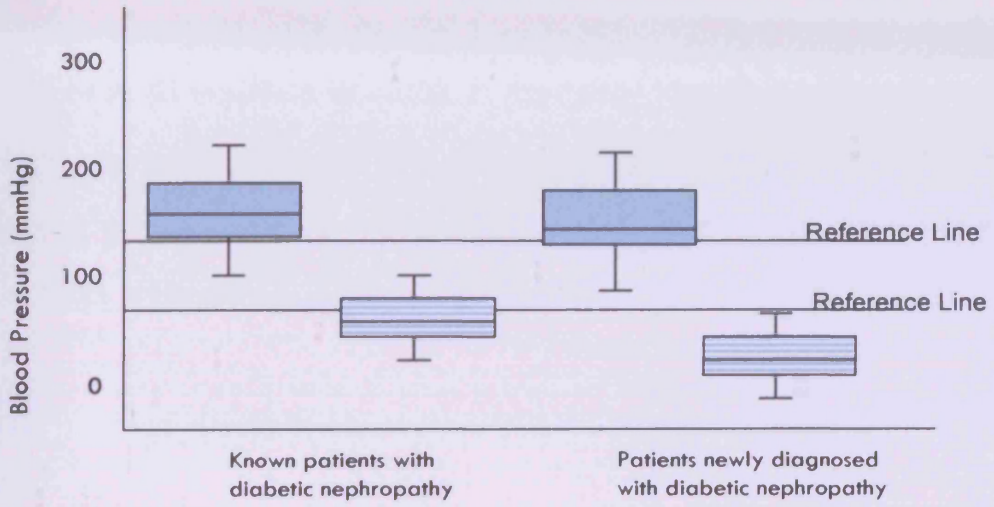


Differences between known and newly diagnose diabetic nephropaths

The distribution of systolic blood pressure and diastolic blood pressures in the known nephropaths and the newly identified nephropaths in shown in Figure 23. There were no statistically significant differences in the blood pressure recordings of patients with known and newly diagnosed nephropathy. Systolic blood pressure guidelines (<135 mmHg) were met by 31% of all known nephropaths, and 26.5% of newly diagnosed nephropaths. Diastolic Blood Pressure guidelines (<75 mmHg) were met by 36% of all known nephropaths and 38% of newly diagnosed nephropaths. However the median, (25th and 75th centile) measures of both systolic and diastolic pressures reflect the fact that 50% of measurements were tightly grouped –

- Known nephropaths Systolic BP 142(133-160): Diastolic BP 80(70-85)
- New nephropaths Systolic BP 149 (137-174): Diastolic BP 77.5 (70-82).

Figure 23 Systolic (solid shapes) and Diastolic (striped shapes) blood pressure of known nephropaths (Phase I and II) and newly identified nephropaths (Phase II).



Use of ACEI inhibitors

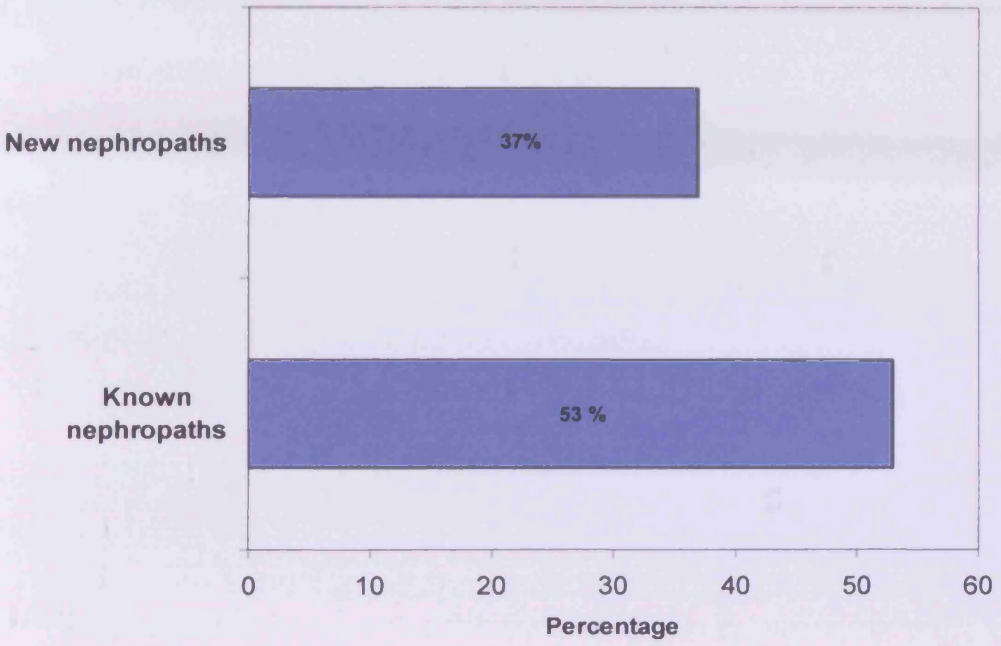
In the patient group of known nephropaths from Phase I and II, 63% were prescribed ACEi inhibitors or ARBs. Of those patients who did not meet the guidelines for blood pressure target of <135/75, 24% were not receiving ACEI inhibitors or ARBs (Table 6).

Use of ACEi inhibitors or ARBs in the newly identified nephropathy patient cohort from Phase II, was 48% and is illustrated in Figure 24. In this patient cohort, of those who did not meet the guidelines for blood pressure target of <135/75, 47% were receiving ACEi or ARBs.

Table 6: Blood pressure control and use of Angiotensin inhibitors (ACEi)/Angiotensin Receptor Blockers (ARB) in the known and newly identified patients with diabetic nephropathy.

	Phase II- known nephropaths n=134	**Phase II-newly identified nephropaths n=40**
Mean SBP (mmHg)	**140** (130-154)	**140** (133-157)
Mean DBP (mmHg)	**78** (70-80)	**80** (70-81)
% of patients with BP>135/75 not on ACEi /ARBs	26.3 %	53.6 %

Figure 24: Prescription of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the newly diagnosed and known nephropaths.



3.5 Management of hypercholesterolaemia

There was no difference in the median cholesterol, LDL, HDL cholesterol nor triglycerides levels between the known and newly identified nephropaths (Table 7). For the known nephropaths 35% had total cholesterol greater than 5.2 mmol/l, In this group statins were prescribed for only 31% of the patients. Similarly elevated cholesterol (total cholesterol >5.2 mmol/l) was documented in 37.5% of newly identified nephropaths, of whom only 9% were prescribed statins.

Table 7: Lipid profiles of diabetic nephropaths.

	All known nephropaths n=249	Phase II-newly identified nephropaths n=40
Cholesterol (mmol/l)	4.6 (3.9-5.0)	5.0 (4.6-5.5)
Triglycerides (mmol/l)	2.2 (1.6-3.2)	2.5 (1.8-3.2)
HDL cholesterol (mmol/l)	1.1 (0.9-1.3)	1.2 (1.0-1.5)
LDL cholesterol (mmol/l)	2.2 (1.8-2.7)	2.6 (1.9-3.0)

3.6 Use of Aspirin

Following publication of the HOT study, the clinic protocol for the treatment of hypertension has included prescription of low dose aspirin to hypertensive diabetics. Analysis of patient records and direct questioning of patients however demonstrated that aspirin was prescribed in only 38% of known nephropaths with hypertension and 43% of newly diagnosed nephropaths with hypertension.

3.7 Discussion

The ever-increasing incidence of diabetic nephropathy has major implications for both patient welfare and health care resources at a time when renal services are already struggling to cope with current demand. The ominous significance of renal involvement in Type I is shown by the comparison of long term outcome in patients with and without nephropathy. Only 10% of patients with proteinuria survive after 40 years of diabetes, in contrast to more than 70% of those without proteinuria [94]. Furthermore the mortality rates for diabetic patients on end-stage renal failure programs is roughly twice that for patients with end stage renal diseases from other causes [86]. Numerous treatment strategies have however been identified which delay the progression of renal disease in diabetes. Significantly in these studies, delay in the progression of renal disease is also associated with improved patient survival [95].

With guidelines setting strict targets for the treatment of nephropathy [93] and increasing evidence that earlier intervention may benefit this patient group [96], [97], it is obvious that clear and effective implementation strategies are required. If successful, it is likely that this would significantly improve both the patient quality of life and life expectancy. Furthermore any reduction in the prevalence of end stage renal failure in diabetes mellitus could have a major impact on the economics of health care provision.

The implementation of evidence based therapeutic interventions in diabetes, outside the confines of a clinical trial have however proved difficult [98]. One

factor implicated in this is the late referral of diabetic patients to specialist renal clinics, as highlighted by the publication of Burton et al [99]. This study demonstrated that the majority of patients were referred at a time when complications of renal failure were already present and that late referral was associated with sub-optimal clinical management of renal disease, in particular a poor outcome on dialysis. What is also clear it that the transfer of care to specialist renal centres may delay the progression of diabetic nephropathy and improve patient morbidity in the forty percent of patients who develop renal disease [87].

Generally, data show that the translation of best practice from both clinical trials and published guidelines into pragmatic clinical practice is difficult and incomplete. One factor suggested to be important is the paucity of resources, especially of non-physician personnel. Many initiatives have demonstrated that the use of physician directed nurse led case management of patients both in improving the glucose management aspect of the delivery of diabetes care and in the aftercare of other chronic conditions [98] [100] [101] [102]. One study has shown that although baseline screening rates for diabetic nephropathy are improving in the U.S.A. the introduction of nurse care management can improve these rates further [102]. The results of this current study support these observations.

The appointment of a nurse to co-ordinate screening had specific aims, namely

- To act as a resource to undertake and coordinate care
- To simplify the operationalisation of the system for microalbumin screening and increase patient compliance
- To act as an education resource for medical staff in secondary care, in particular to ensure that more junior staff were well informed and to highlight gaps in therapy
- With support from medical staff, to act as a resource for primary care physicians and nurses using seminars to disseminate best practice and assist in the practical aspects of improving screening
- To act as an educational resource for the patient cohort, ensuring that this improves returns for microalbumin screening.

Previous studies have demonstrated that the quantification of the urinary albumin to creatinine ratio in a random single voided urine sample is a reproducible alternative to the formal quantification of urinary protein loss [92]. Using this approach, a cohort of diabetic patients with nephropathy was identified, in whom the diagnosis had not been made by existing clinical practice, and therefore appropriate intervention could not have been initiated. Interestingly there were no significant differences between the nephropaths diagnosed by the existing protocol and the additional newly identified group of patients detected by the nurse led screening program. Specifically the newly identified group were not those with recent onset of Diabetes Mellitus but came from the same population as those who were known nephropaths and

may therefore truly have been 'missed'. The discrepancy in the assumed and true prevalence of diabetic nephropathy has identified numerous levels at which screening practice was failing to identify patients with diabetic nephropathy. Although screening was targeted to all patients, compliance in terms of return of urine samples resulted in numerous missed patients. Furthermore, failure of documentation, even in those in which the screening program did lead to a diagnosis of nephropathy, led physicians to be unaware of the diagnosis at the time of patient consultation.

Another factor which hampers the introduction of structured care protocols is patient compliance. Studies aimed at starting an intensive lipid-lowering strategy in patients with diabetes mellitus demonstrated the importance of patient perceptions of treatment benefits as only 12% of their patients participated in the study [103]. Nurse led initiatives in diabetes care in general practice, however, have shown benefit to patients in terms of clinical management and also significantly in patient satisfaction [101]. Following instigation of prospective screening, albumin: creatinine ratio was used to target those patients for quantification of urinary albumin excretion at the time of their clinic visit. To improve patient compliance, all patients with raised urine albumin: creatinine ratios in the random urine samples were seen by the designated nurse and counselled as to the importance of further urine albumin quantification. Furthermore, patients who failed to provide urine samples for formal quantification of urinary albuminuria were contacted again by the nurse.

The excess morbidity and mortality in diabetic patients requiring renal replacement therapy is explained by high cardiovascular co-morbidity, and survival on dialysis is largely determined by pre-dialysis care [104] In terms of minimising cardiovascular risk, analysis of the UK Prospective Diabetic Study (UKPDS) and the diabetic sub-group of the Hypertension Optimal Treatment (HOT) trial has provided clear evidence that control of blood pressure reduces the risk of cardiovascular events [105] [80]. The targets for optimum blood pressure control have been decreasing steadily over the last ten years, but the plethora of differing targets have led to difficulties for clinicians and patients in keeping abreast of changes. Furthermore analysis of diabetic patients recruited into the Heart Outcomes Prevention Evaluation (the MICRO-HOPE) study suggested a specific cardio-protective action of drugs that block the renin-angiotensin system [36]. Analysis in secondary prevention studies also suggests beneficial effects of treatment of hypercholesterolaemia [106] [107]. Finally studies have also confirmed that aspirin prevents cardiovascular events both in hypertensive [80] and diabetic individuals These data demonstrate that in a cohort of patients identified as diabetic nephropaths and therefore at high cardiovascular risk, prescription of therapeutic measures aimed at both delaying the rate of progression of renal disease and targeted at cardiovascular risk is poor. From the point of view of progression of renal disease, it is of particular note that a large proportion of the patients did not meet published blood pressure guidelines. Furthermore, the use of ACEi in the group of patients with sub-optimal blood pressure control is also low and represents a missed opportunity in terms of minimising risk of progression of renal disease and addressing cardiovascular risk factor

management. It is likely that documentation in the patient records of positive urinalysis in only 50% of cases in part, at least, explains the low ACEi prescription rates in known diabetic nephropaths. It is not unexpected however that in those "missed" nephropaths that were identified following change of practice, ACEi usage was particularly poor. The significant omission of ACEi in the subgroup of hypertensive "missed" nephropaths however, further emphasises the need for a comprehensive and effective screening program. Having significantly improved identification of this "high risk" population, examination of the impact of a nurse led management programme on achieving accepted treatment targets formed the next step of this intervention.

It is acknowledged that many 'lifestyle' factors have a substantial impact on the cardiovascular risk of the population including

- Weight and Body Mass Index
- Alcohol consumption
- Smoking
- Glycaemic control

Modification of these risk factors are an essential part of the management of cardiovascular risk but were beyond the scope, remit and resources of these projects but are tackled on a routine basis by diabetic specialist nurses, in both primary and secondary care.

Chapter 4:

A stepwise, nurse-led intervention algorithm: Impact over twelve months on Blood Pressure control and Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptors Blocker prescription in a patient cohort with Diabetic Nephropathy.

4.1 Introduction

The previous chapter has highlighted the deficiencies in care for this patient cohort with diabetic nephropathy and has led to the recognition that an assessment of the current mode of care delivery in this context is required and introduction of an alternative mode of care delivery should be undertaken. As has also been noted, the benefit and importance of blood pressure control and therapy with Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (AR Blockers) has been clearly demonstrated from evidence in the published literature. In response to this evidence, the aim of this chapter is to describe the introduction and outcomes of nurse led, algorithm driven practice which integrated primary and secondary care and attempted to improve blood pressure control and ACEi/AR Blockers in this vulnerable group of patients.

4.2 Patient Cohort

All enrolled patients attended the diabetes clinic led by a single Diabetologist based at a teaching hospital. A newly appointed dedicated specialist nurse discussed study entry with all nephropaths from consecutive patients seen in the diabetic clinic over an 8-month period, as reported in the previous chapter. All prescribed medication was recorded, and in particular, the use of ACEi, angiotensin II receptor blockers (ARBs) and number of antihypertensive medications.

4.3 Blood Pressure Recording

An algorithm was designed to assist and standardise the identification of all patients with sub optimally controlled blood pressure. The nurse then ensured that clinic medical staff were informed of patients requiring changes in therapy (Figure 14). This algorithm stratified patients based on their initial blood pressure reading at that clinic visit. If blood pressure was above treatment guidelines a repeat measurement was done 30 minutes later. Based on this second reading those patients with blood pressure >140/80mmHg were targeted for intensification of their blood pressure medication. Patients with borderline hypertension (>135/80 mmHg but <140/80 mmHg) had a 24-hour blood pressure monitor fitted to identify those with blood pressure readings outside guidelines. The algorithm had a detailed stepwise phased introduction of agents to attain blood pressure control taking account of existing comorbid conditions.

Clinic blood pressure was measured with an automated digital blood pressure monitor (Omron Healthcare UK, Henfield, West Sussex, UK) after a 5-minute seated rest.

For patients above target (either systolic, diastolic or both), treatment changes were initiated, where possible, in the diabetic clinic. There were occasions however, when it proved difficult to initiate change in the clinic, sometimes due to the patient not being seen by the specialist nurse prior to their appointment and on other occasions by the reluctance of the medical staff to comply with the algorithm but choosing to rely upon their own clinical judgement instead. In patients where this was the case, the link between the nurse specialist and

the Primary Care team was utilised to bring about treatment change and monitor progress and response to changes in therapy.

In addition to the Clinical Nurse Specialist and the Primary Care Team a Consultant Nephrologist was available to offer additional advice about treatment changes or difficult management decisions. Follow up was arranged with primary care and information from the follow up visits was fed-back to the Clinical Specialist Nurse. Once blood pressure was at target the patients were then seen 3 monthly by the practice nurse.

All patients with blood pressure measurement at or below target were allocated to routine follow up care comprising annual follow up in the diabetic clinic.

Although the role of both Mean Arterial Pressure (MAP) and Pulse Pressure (PP) remain controversial in the prediction of cardiovascular risk, it was felt appropriate to report the range of values in this patient cohort. Mean arterial pressure (MAP) was calculated using the formula MAP = [(2 x diastolic)+systolic] / 3. A MAP of about 60 is necessary to perfuse coronary arteries, brain and kidneys, with the usual range being between 70 and 110 mmHg. The role of pulse pressure in the prediction of cardiovascular risk was considered as part of an analysis from data collected as part of the Framingham study and published in the late 1990s [108]. The authors concluded that in the middle-aged and elderly, cardiovascular risk increased with lower DBP at any level of SBP≥120 mm Hg, suggesting that higher PP was an important component of risk. Neither SBP nor DBP was superior to PP in predicting CHD risk

4.4 Results

A total of 233 patients from the original cohort of patients with diabetic nephropathy agreed to take part in the second phase and were recruited into the study with complete data available on 222 patients. The median (IQR) age of the patients in the study was 66(57-73) years and the gender ratio was 153:80 (M: F). There were 203 type 2 diabetic patients and 100 of these patients required insulin. All patients were followed up for at least 12 months.

4.4.1 Blood Pressure: the total population

Baseline Measurements:

Systolic and diastolic blood pressure was measured using the algorithm detailed in Figure 14. After every participant had been in the study for a minimum of twelve (12) months, measurement was made of blood pressure parameters, Angiotensin Converting Enzyme Inhibitor (ACEi) and Angiotensin Receptor Blocker use.

In the population as a whole, Median (Inter Quartile Range) systolic blood pressure was 145(133-160) mmHg at study start and 145(135-160) mmHg at study end and is illustrated in frequency charts 24a and 24b.

Median (IQR) Diastolic Blood pressure was 80(70-88) mmHg at study start and 76(68-84) mmHg at study end for the total group and is illustrated in Figures 25a and 25b.

Statistical analysis was undertaken using Wilcoxon Signed Rank Test and showed no statistically significant difference (p=0.836) between the two measurements for systolic blood pressure and p=0.056 for diastolic blood pressure.

Box and whisker plots (Figures 26 and 27) of systolic and diastolic blood pressure of the total population illustrates the distribution in the total population.

The median (IQR) of Pulse Pressure (PP) and Mean Arterial Pressure (MAP) in this cohort of patients at the start of the intervention were 100.3(93.3-110)

mmHg and 70(55-81) mmHg respectively. At study end, MAP was 98.7(92-108) and Pulse Pressure was 70(58-82) mmHg. Frequency charts of Mean Arterial Pressure and Pulse Pressure are illustrated in Figures 28a and 28b; Figures 29a and 29b respectively. Box and Whisker plots (Figures 30 and 31) illustrate the Median (IQR) of Mean Arterial Pressure and Pulse Pressure respectively

Proportion of patients meeting guidelines

Analysis of the total population was undertaken to ascertain the proportion of patients meeting the current guidelines for Systolic Blood Pressure (equal to or less than 135 mmHg) and Diastolic Pressure (equal to or less than 75 mmHg) and is illustrated in Table 8.

Table 8: Numbers of patients meeting and not meeting Systolic and Diastolic Targets

	At diastolic target	Not at diastolic target
At systolic target	39	27
Not at systolic target	43	113

In summary, 39 (17.6%) patients met both systolic and diastolic targets, 43 (12.1%) patients had isolated systolic hypertension, whilst 113 (50.9%) patients met neither systolic nor diastolic targets.

For the purposes of further analysis, patients were divided into those that met both targets (n=39) and those who did not meet either systolic or diastolic targets or both (n=183).

Figure 24a: Frequency Chart of Systolic Blood Pressure for total population at study start

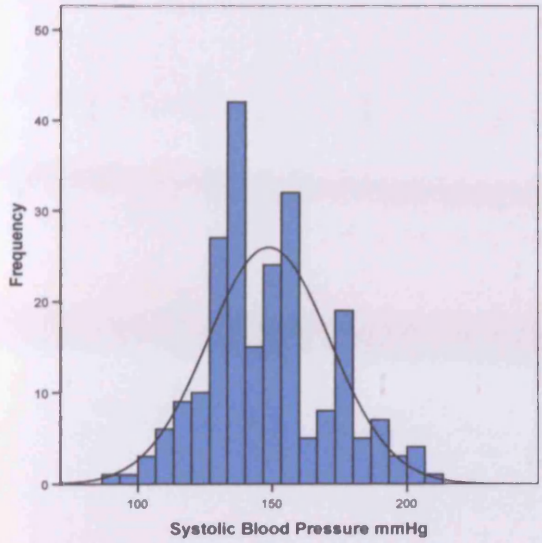


Figure 24b: Frequency Chart of Systolic Blood Pressure for total population at study end

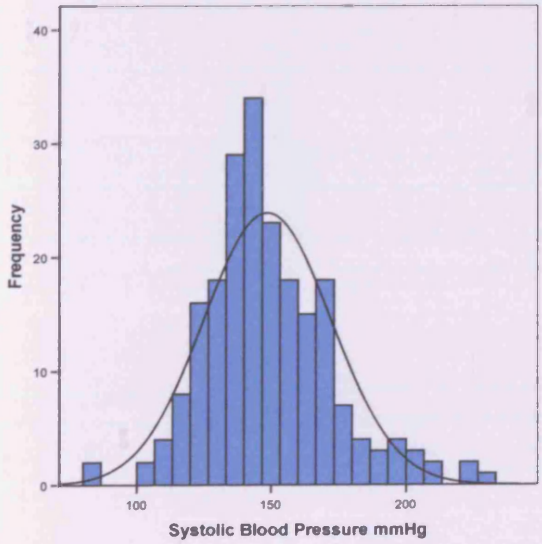


Figure 25a: Frequency Chart of Diastolic Blood Pressure for total population at study start

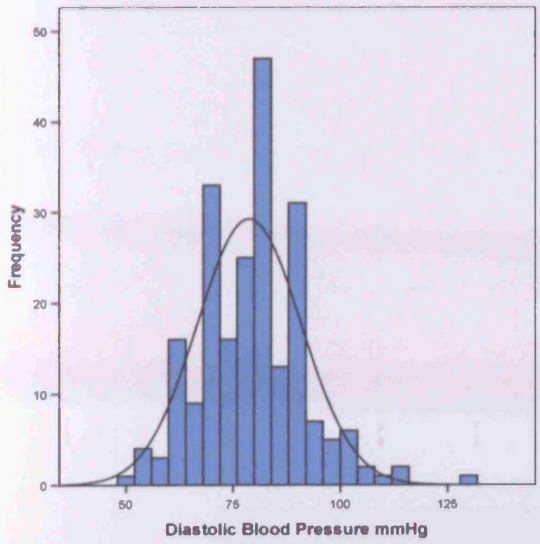


Figure 25b: Frequency Chart of Diastolic Blood Pressure for total population at study end

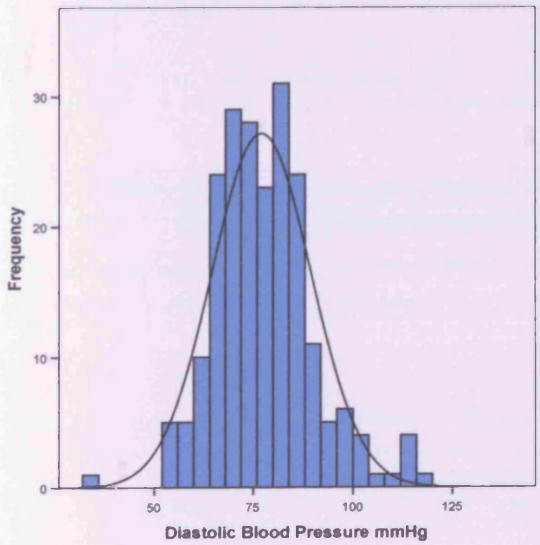


Figure 26: Systolic Blood Pressure at study start and end for the total population

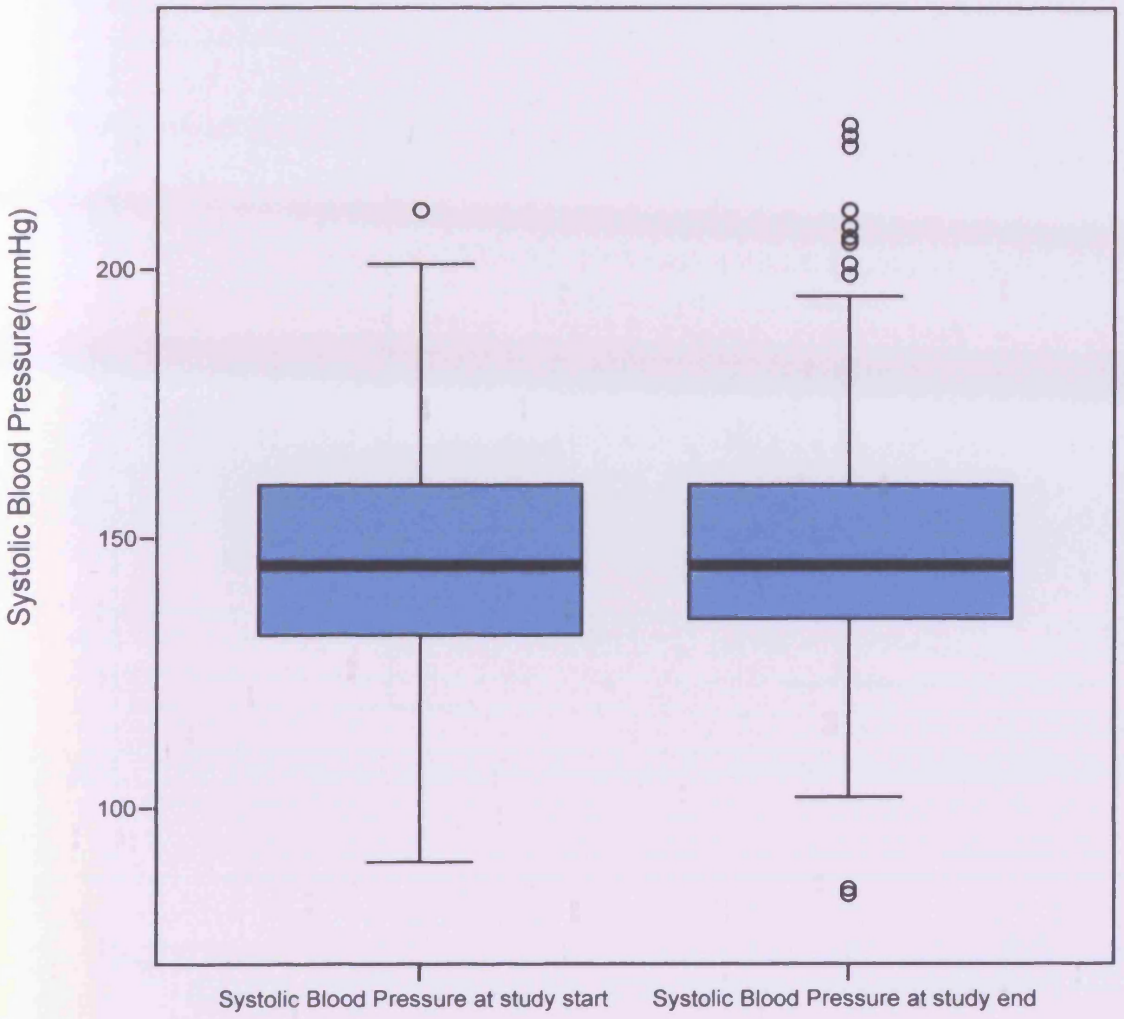


Figure 27: Diastolic Blood Pressure at study start and end for the total population

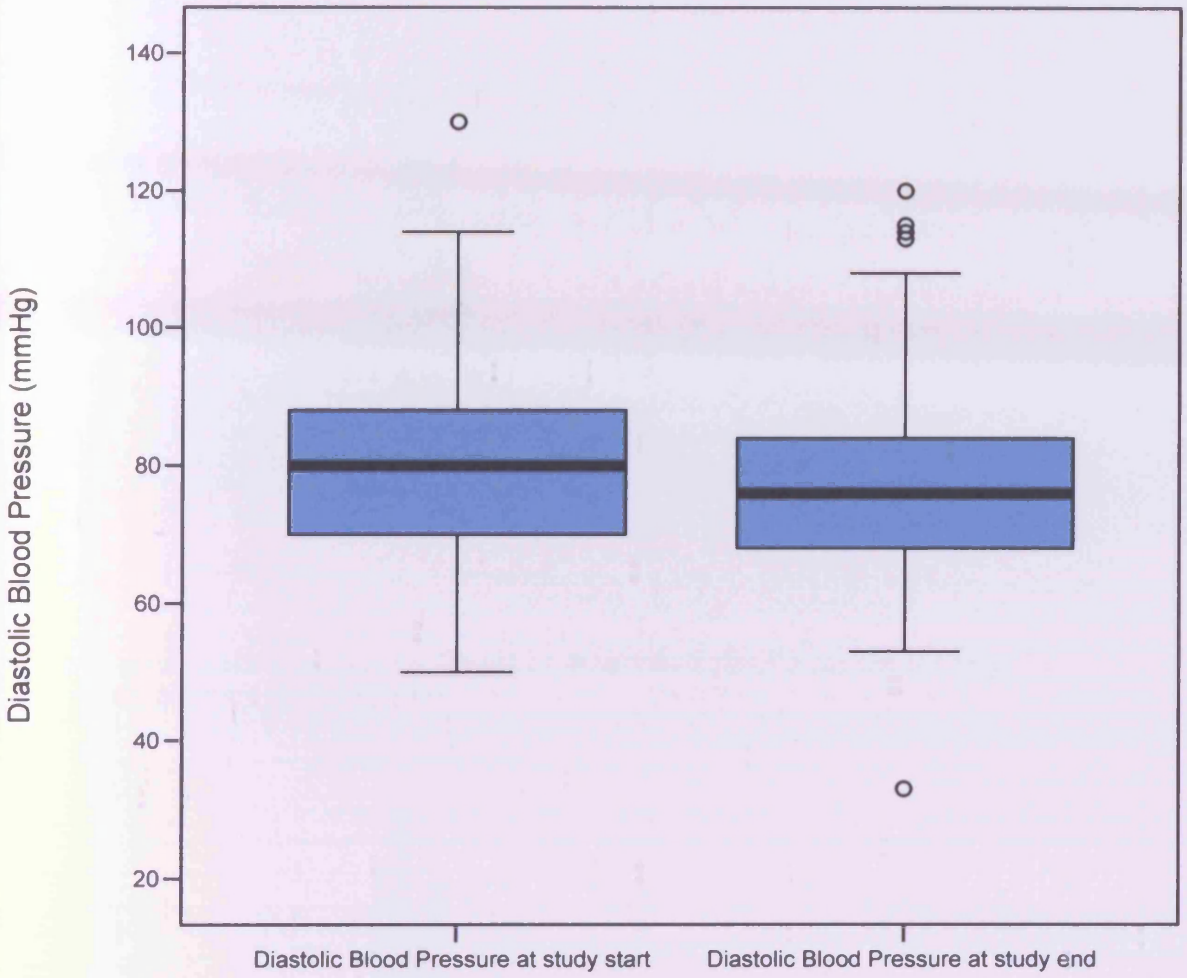


Figure 28a: Frequency Chart of Mean Arterial Pressure for total population at study start

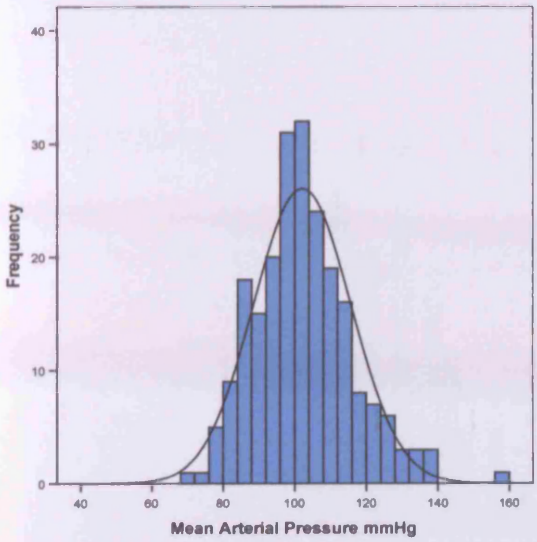


Figure 28b: Frequency Chart of Mean Arterial Pressure for total population at study end

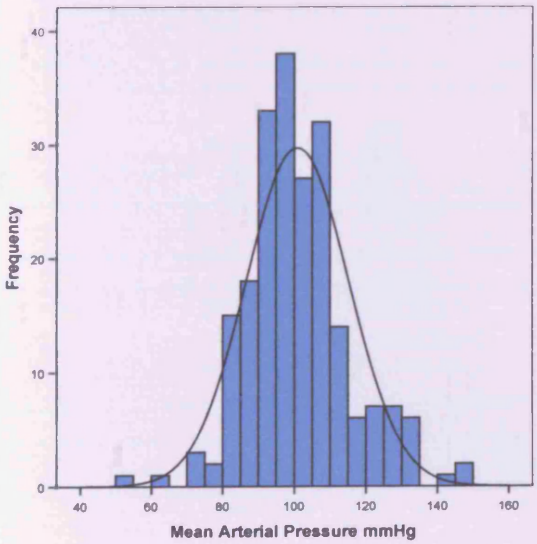


Figure 29a: Pulse Pressure for total population at study start

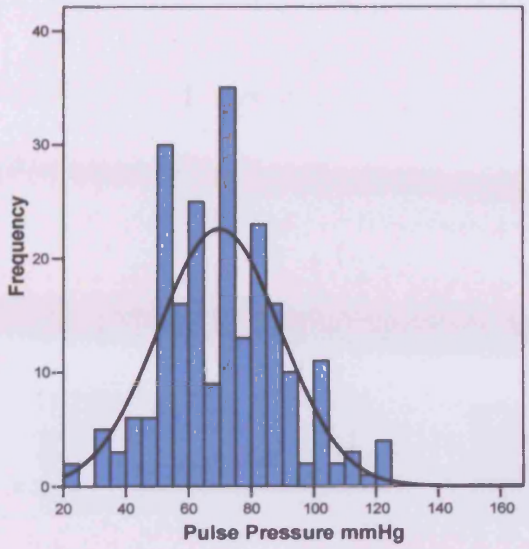


Figure 29b: Pulse Pressure for total population at study end

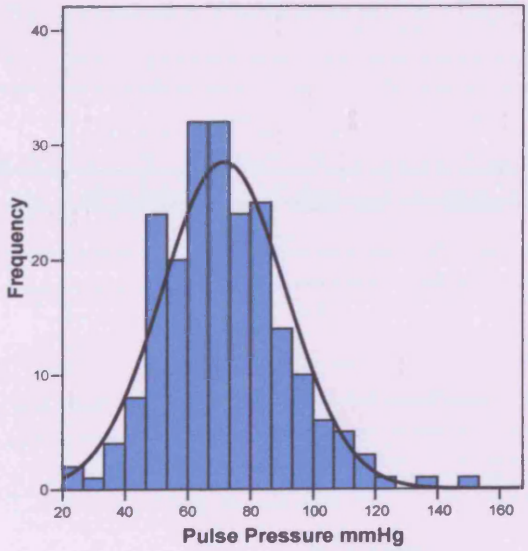


Figure 30: Mean Arterial Pressure at study start and end for the total population

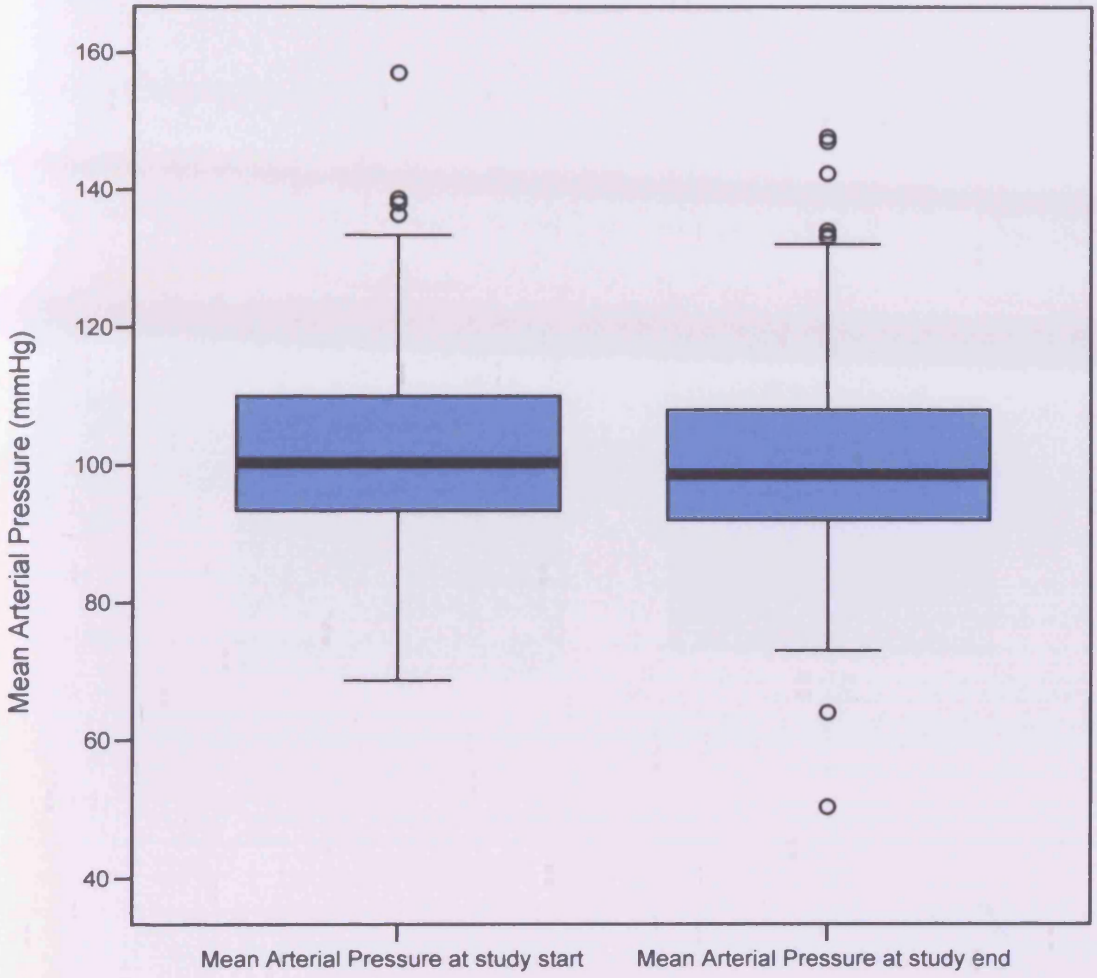
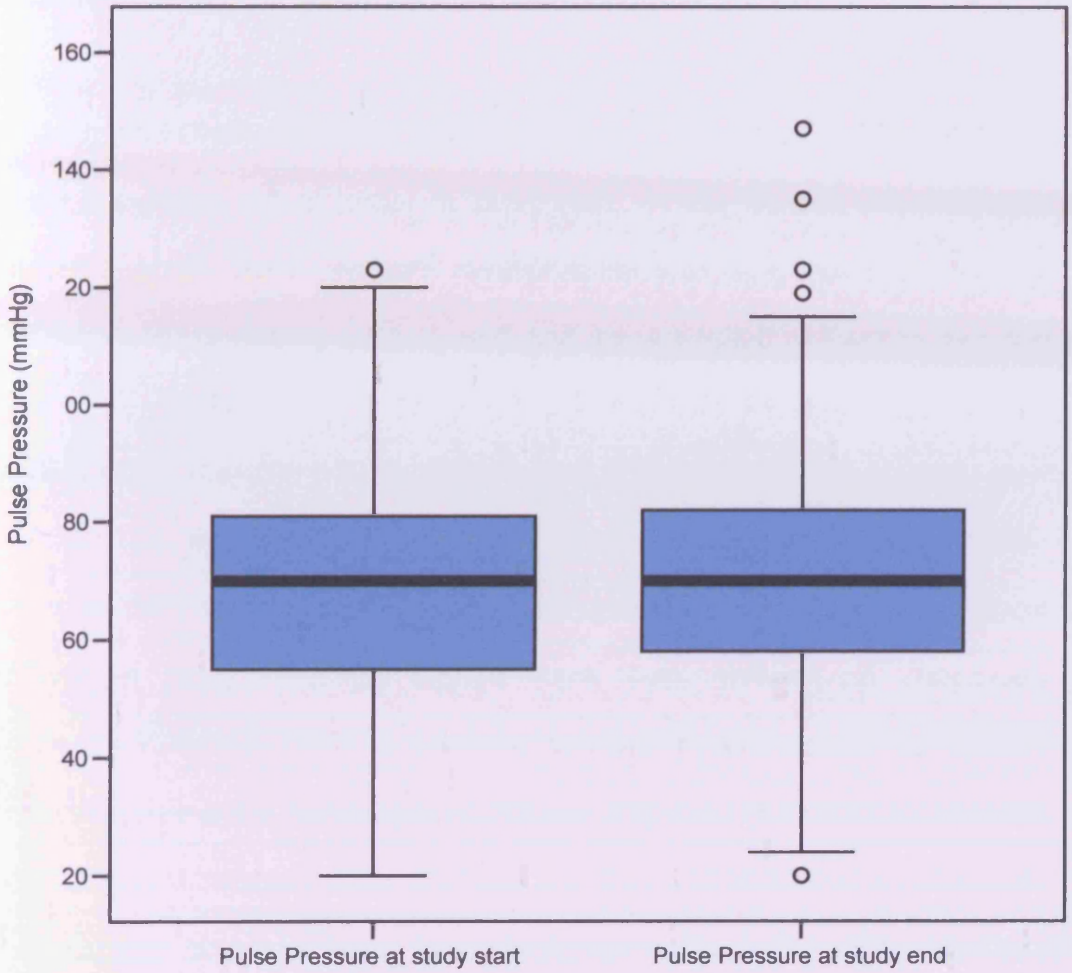


Figure 30: Pulse Pressure at study start and end for the total population



4.4.2 Blood Pressure: the population not at target for systolic, diastolic or both pressures at study start.

Systolic and Diastolic Blood Pressure

In the population not at target at study start, n=183, Median (Inter Quartile Range) Systolic blood pressure measurement was 150(140-167.5) mmHg; 146.5(136-164.5) mmHg at study end and are illustrated in Figures 32a and 32b.

Median (IQR) diastolic blood pressure was 80(77-90) mm Hg at study start and 78(70-85) mmHg at study end and are illustrated in Figures 33a and 33b.

Although both systolic and diastolic blood pressure fell, statistical analysis undertaken using Wilcoxon Signed Rank Test, showed no statistically significant difference (p=0.1) between the two measurements for systolic blood pressure but a statistically significant difference (p=0.002) for diastolic blood pressure between study start and end. Box and whisker plots of systolic and diastolic blood pressure of patients not at target at study start are illustrated in Figures 34 and 35 respectively.

Figure 32a: Frequency Chart of Systolic Blood Pressure at study start: Patients not at target at study start

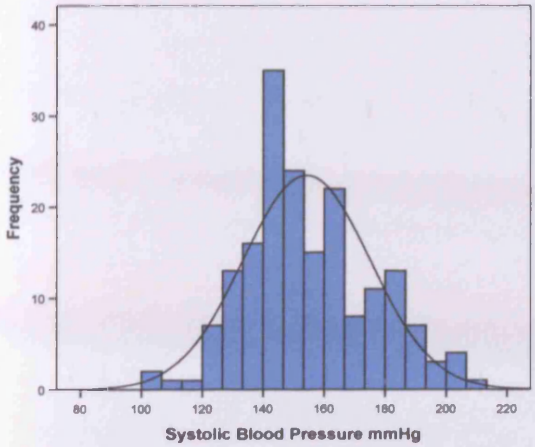


Figure 32b: Frequency Chart of Systolic Blood Pressure at study end: Patients not at target at study start

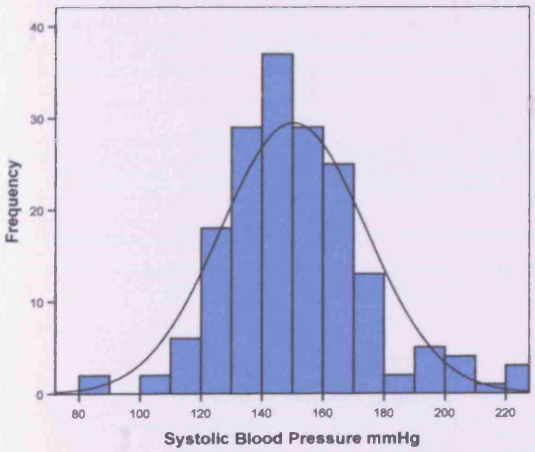


Figure 33a: Frequency Chart of Diastolic Blood Pressure at study start: Patients not at target at study start

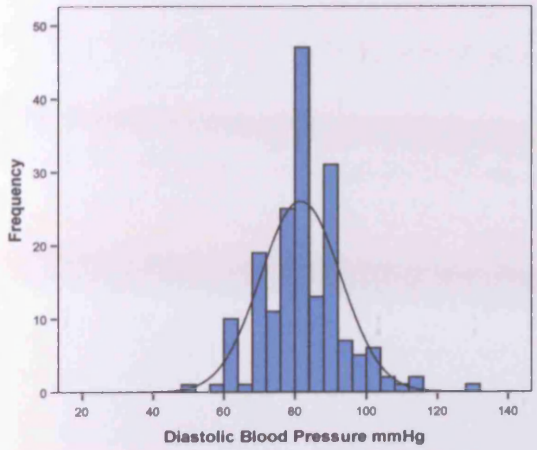


Figure 33b: Frequency Chart of Diastolic Blood Pressure at study end: Patients not at target at study start

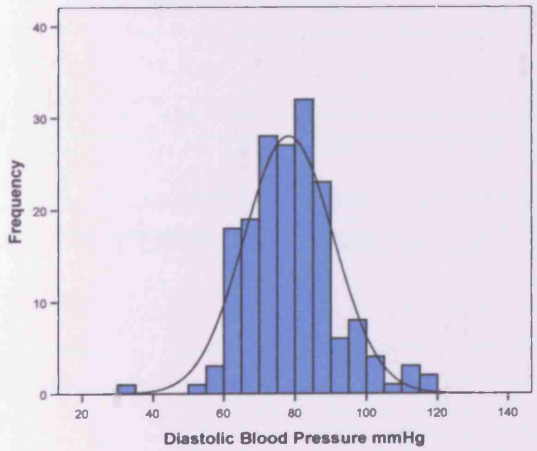


Figure 34: Systolic Blood Pressure at study start and end: patients not at target at study start

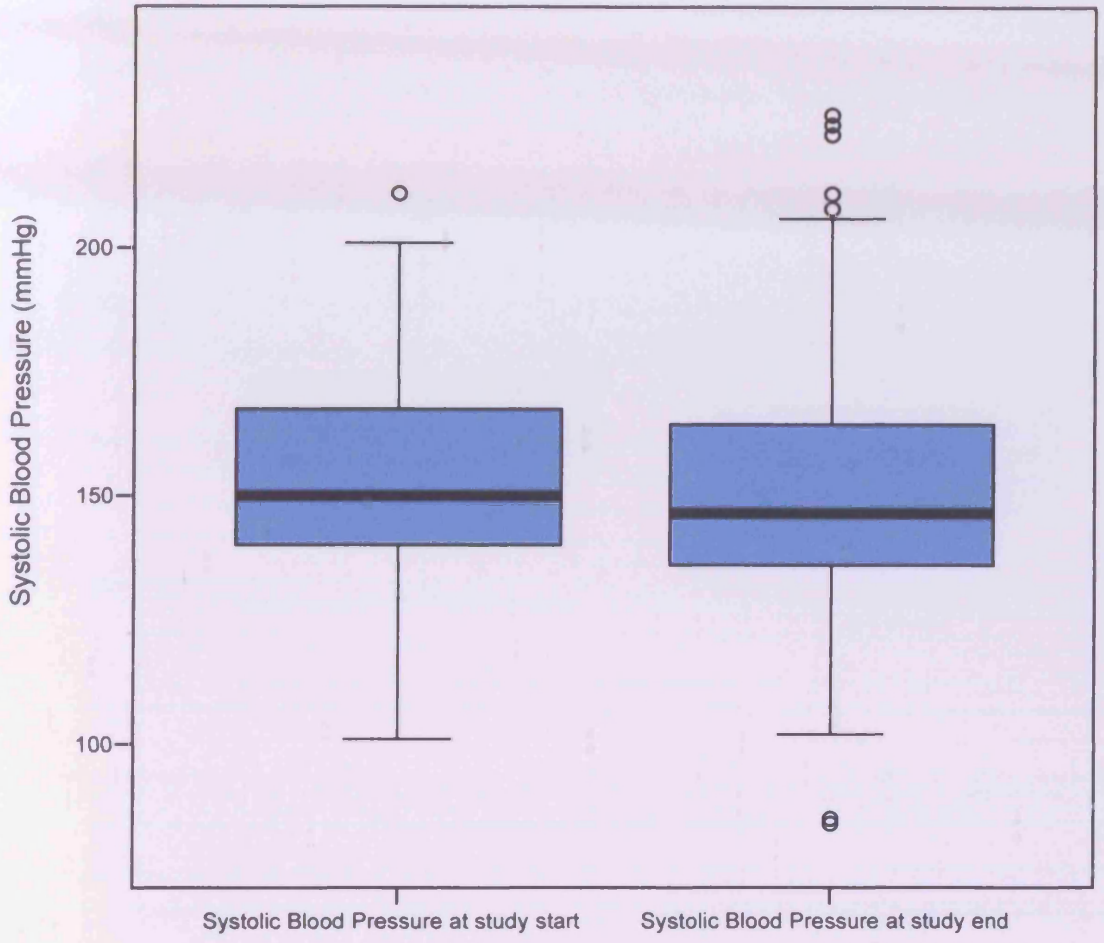
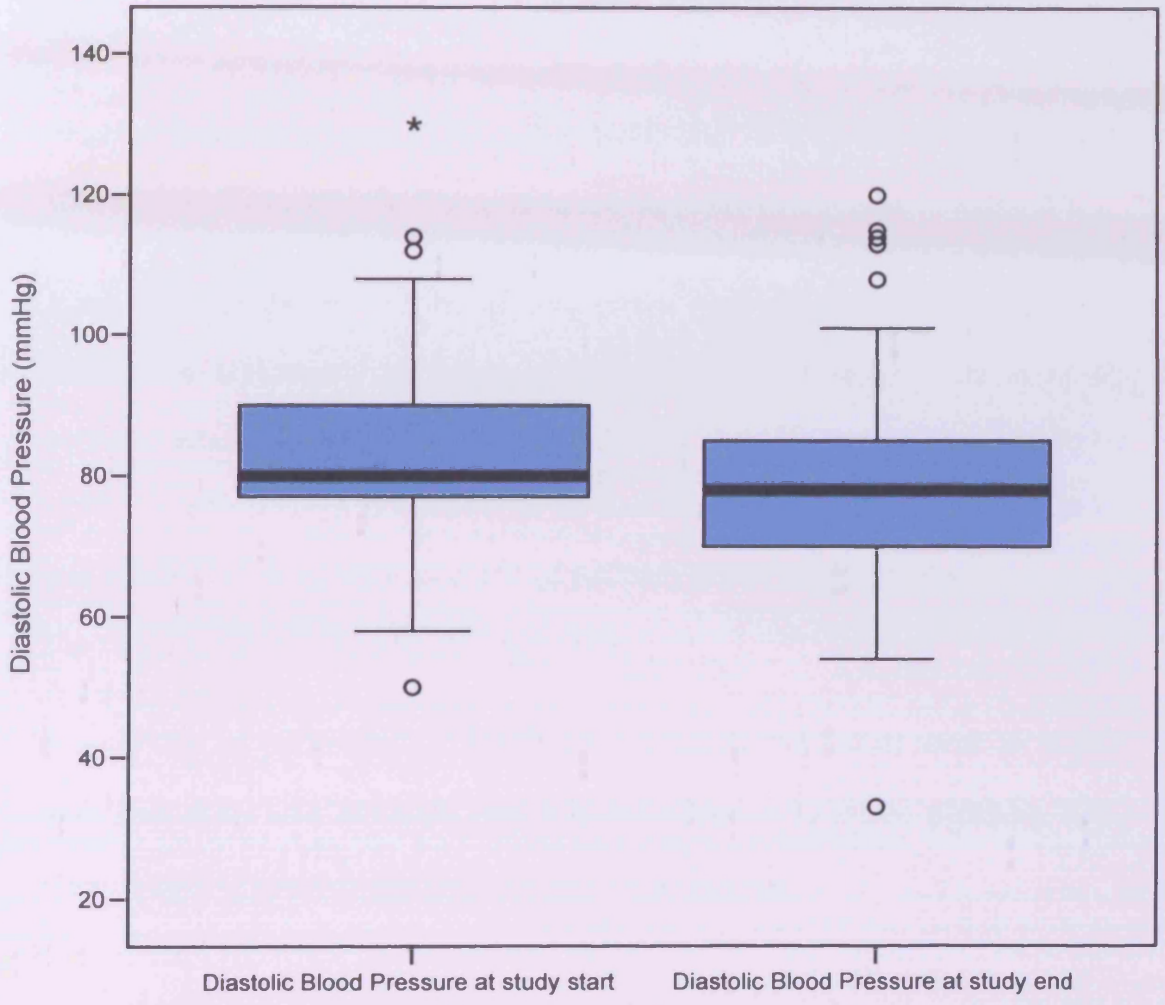


Figure 35: Diastolic Blood Pressure at study start and end: Patients not at target at study start



Mean Arterial Pressure and Pulse Pressure

Mean Arterial Pressure (MAP) was 103.3(98.3-112.8) mmHg at study start and at study end was 100.2(93.7-108.5) mmHg and is illustrated in Figures 36a and 36b.

Pulse Pressure (PP) was 71(57.3-85) mmHg and 70.5(58-84) mmHg at study start and end respectively. These data are illustrated in Figures 37a and 37b.

Again, both MAP and PP fell in this group from study start to study end although a statistically significance difference was detected only in MAP between study start and end using Wilcoxon Signed Rank Test (p=0.011) whilst no difference (p=0.786) could be demonstrated in Pulse Pressure. Box and whisker plots of MAP and PP of patients not at target at study start are illustrated in Figures 38 and 39 respectively

In summary, all parameters of blood pressure were decreased between study start and study end although only the decreases in Diastolic pressure and Mean Arterial Pressure reached statistical significance.

Figure 36a: Frequency Chart of Mean Arterial Pressure at study start: Patients not at target at study start

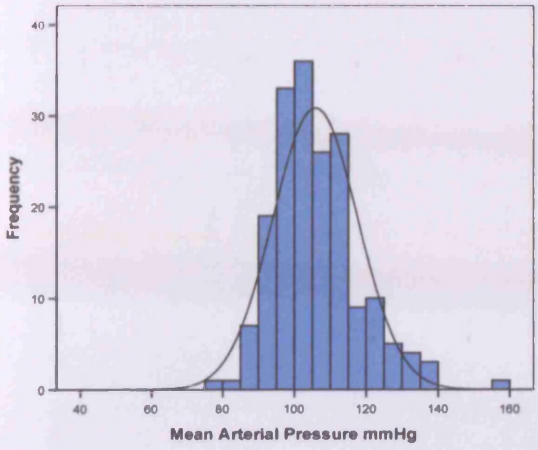


Figure 36b: Frequency Chart of Mean Arterial Pressure at study end: Patients not at target at study start

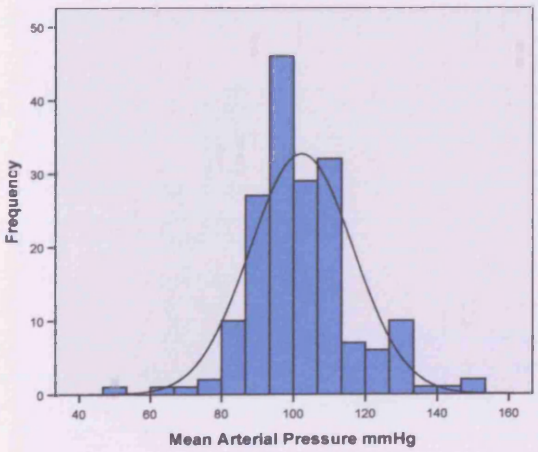


Figure 37a: Frequency Chart of Pulse Pressure at study start: Patients not at target at study start

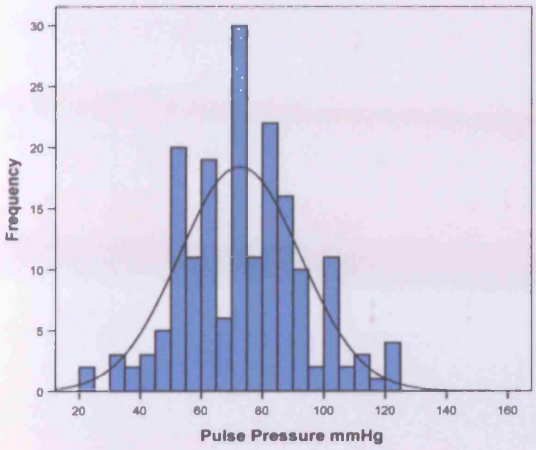


Figure 37b: Frequency Chart of Pulse Pressure at study end: Patients not at target at study start

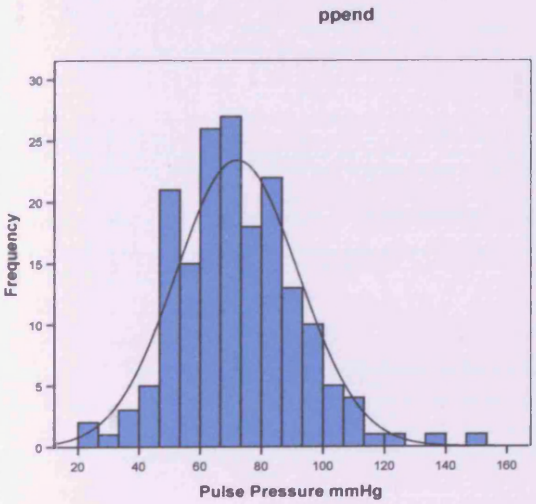


Figure 38: Mean Arterial Pressure at study start and end: Patients not at target at study start

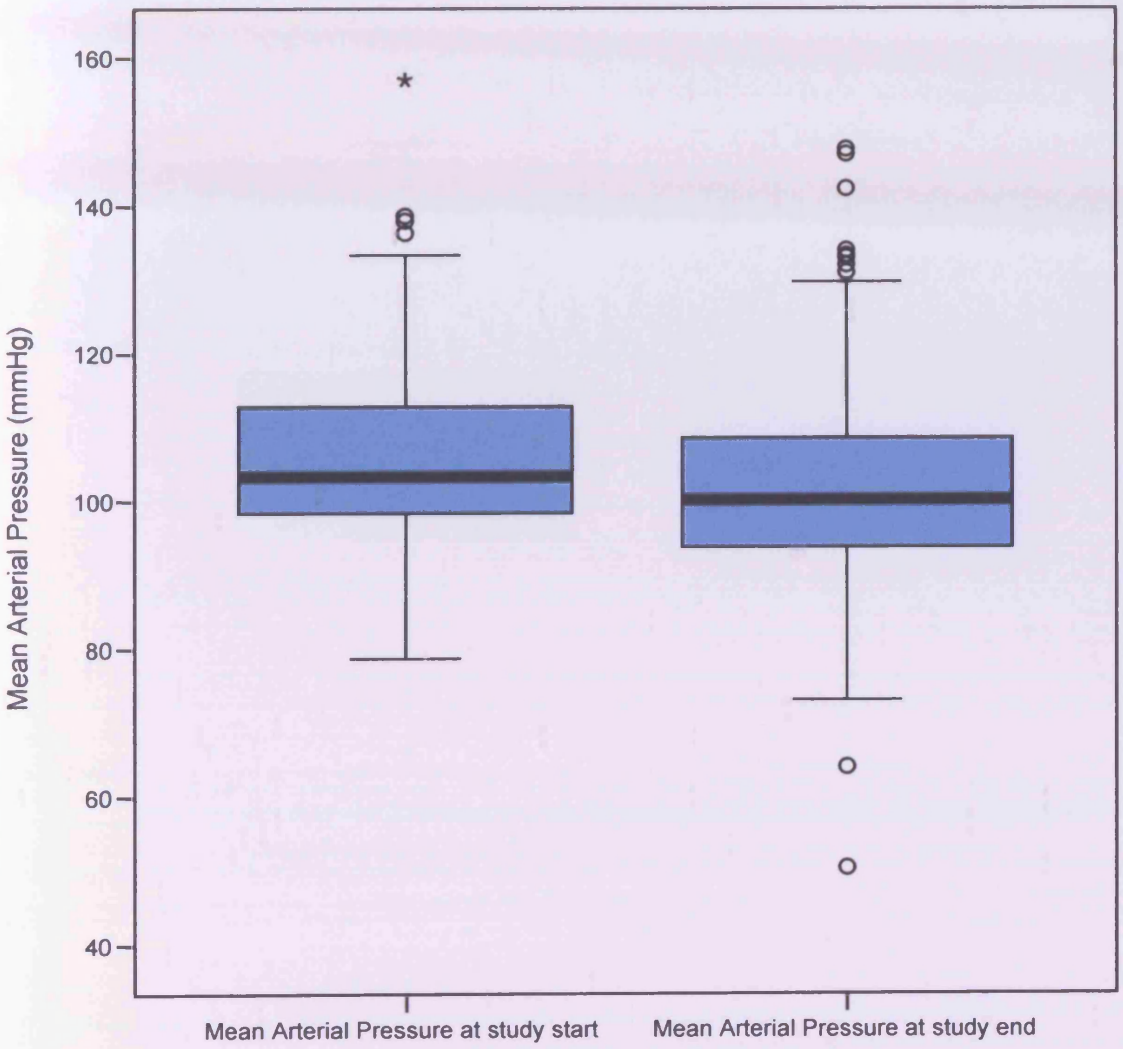
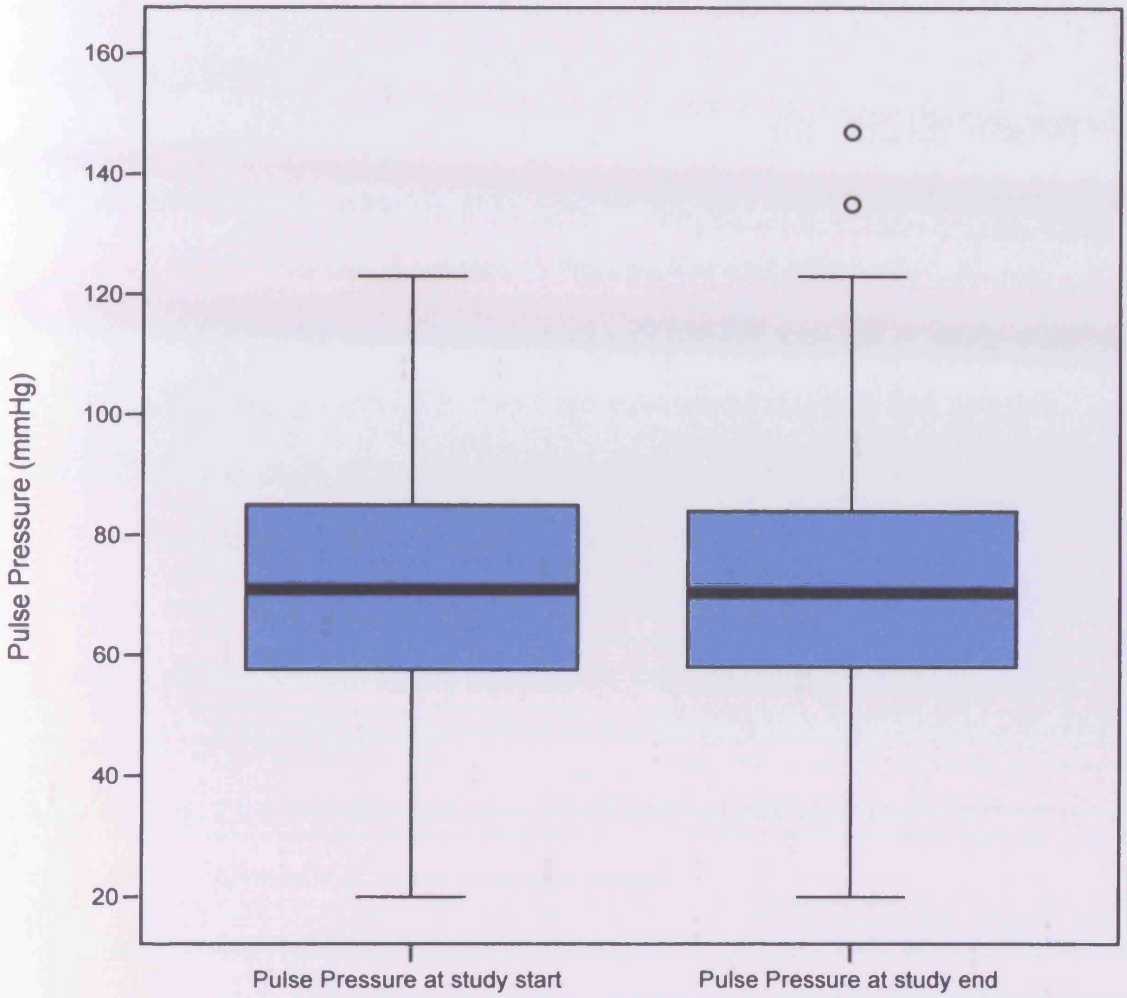


Figure 39: Pulse Pressure at study start and end: Patients not at target at study start



4.4.3 Blood Pressure: the population at target for both systolic and diastolic at study start.

Systolic and Diastolic Blood Pressure

In the population at target at study start, Median (Inter Quartile Range) systolic blood pressure was 127 (117-130) mmHg and 135(128-150) mmHg at study end. These data are illustrated in Figures 40a and 40b.

Median (IQR) diastolic blood pressure was 66(62-70) mm Hg at study start and 71(66-77) mmHg at study end and are illustrated in Figures 41a and 41b.

Box and whisker plots of systolic and diastolic blood pressure of patients at target at study start are illustrated in Figures 42 and 43 respectively

Statistical analysis was undertaken using Wilcoxon Signed Rank Test and showed a statistically significant increase in both systolic pressure ($p<0.001$) and diastolic pressure ($p=0.002$).

By study end, 23 of the 39 patients who had been at target at study start were outside one or both of the blood pressure targets.

Graphical representation of individual changes in both systolic and diastolic blood pressures (Figures 44 and 45 respectively) illustrate that of the 39 patients at target at study start, 32 patients increased their systolic pressure. In addition 31 of the 39 patients had increases in diastolic pressure.

Mean Arterial Pressure and Pulse Pressure

The Median (IQR) of Mean Arterial Pressure (MAP) at study start was 85.6(80.7-91.9) mmHg rising to 93.7 (85.3-101)mmHg at study end and illustrated in Figures 46a and 46b respectively.

Pulse Pressure (PP) in this cohort of patients at the start and end of the intervention were 55 (50-65.5) mmHg and 68(56-77) mmHg respectively. These data are illustrated in Figures 47a and 47b respectively.

Box and whisker plots of Mean Arterial Pressure and Pulse Pressure of patients at target at study start and end are illustrated in Figures 42 and 43 respectively

A statistically significant increase was detected in both Mean Arterial Pressure and Pulse Pressure using Wilcoxon Signed Rank Test ($p<0.001$).

Figure 40a: Frequency Chart of Systolic Blood Pressure at study start: Patients at target at study start

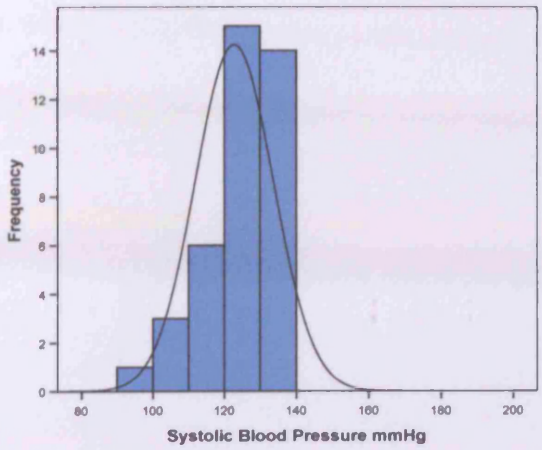


Figure 40b: Frequency Chart of Systolic Blood Pressure at study end: Patients at target at study start

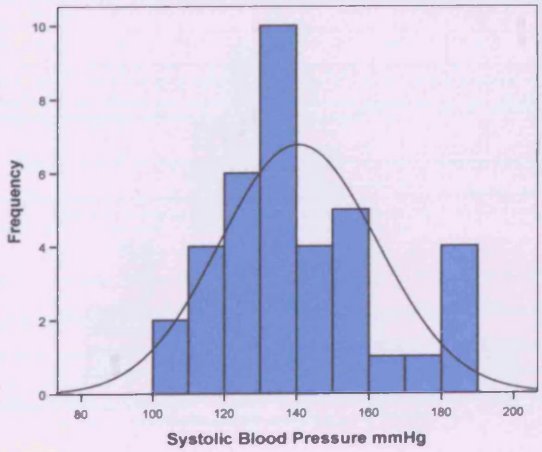


Figure 41a: Frequency Chart of Diastolic Blood Pressure at study start: Patients at target at study start

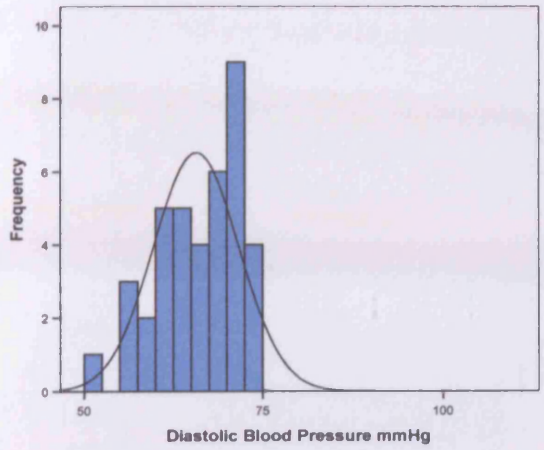


Figure 41b: Frequency Chart of Diastolic Blood Pressure at study end: Patients at target at study start

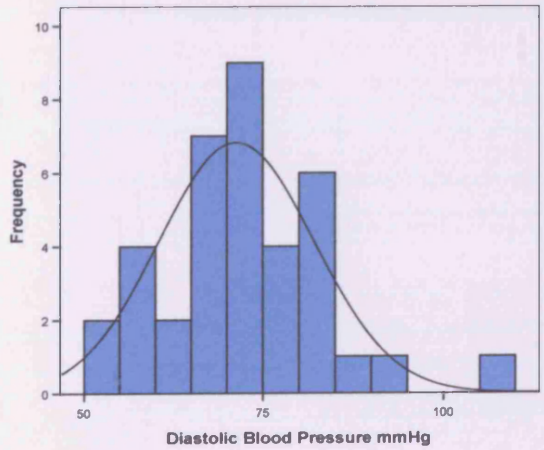


Figure 42: Systolic Blood Pressure at study start and end: Patients at target at study start

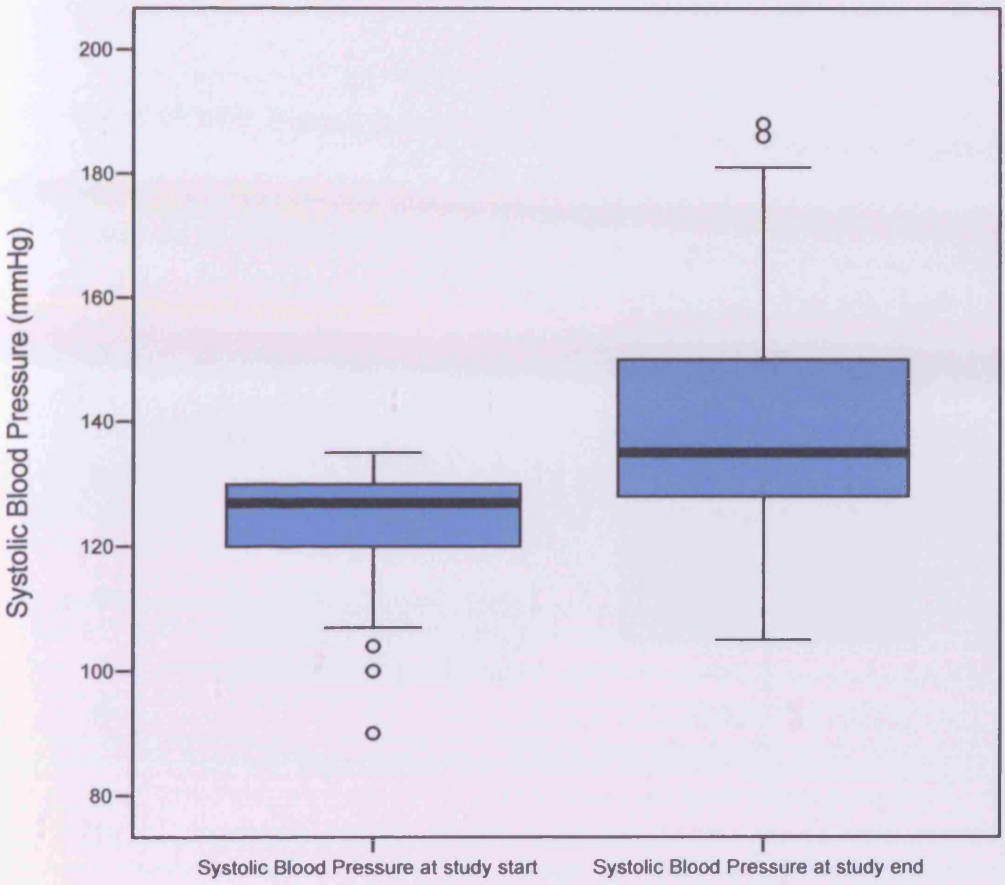


Figure 43: Diastolic Blood Pressure at study start and end: Patients at target at study start

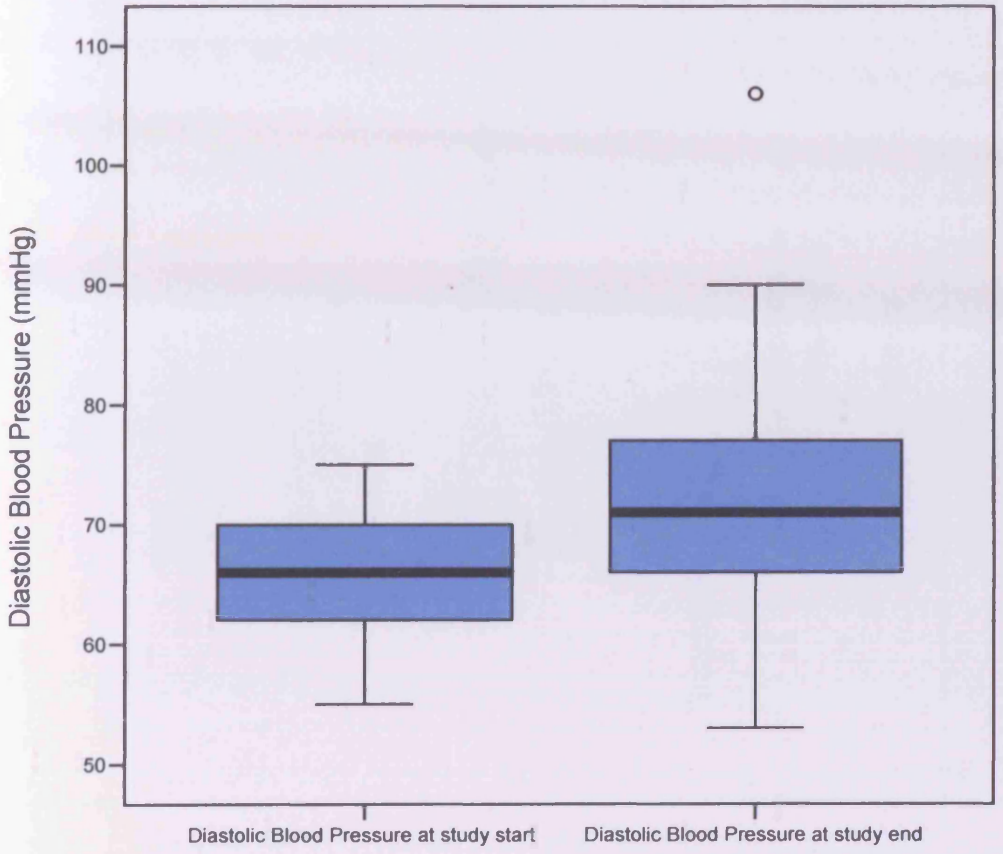


Figure 44: Individual Changes in Systolic Blood Pressure from study start to end

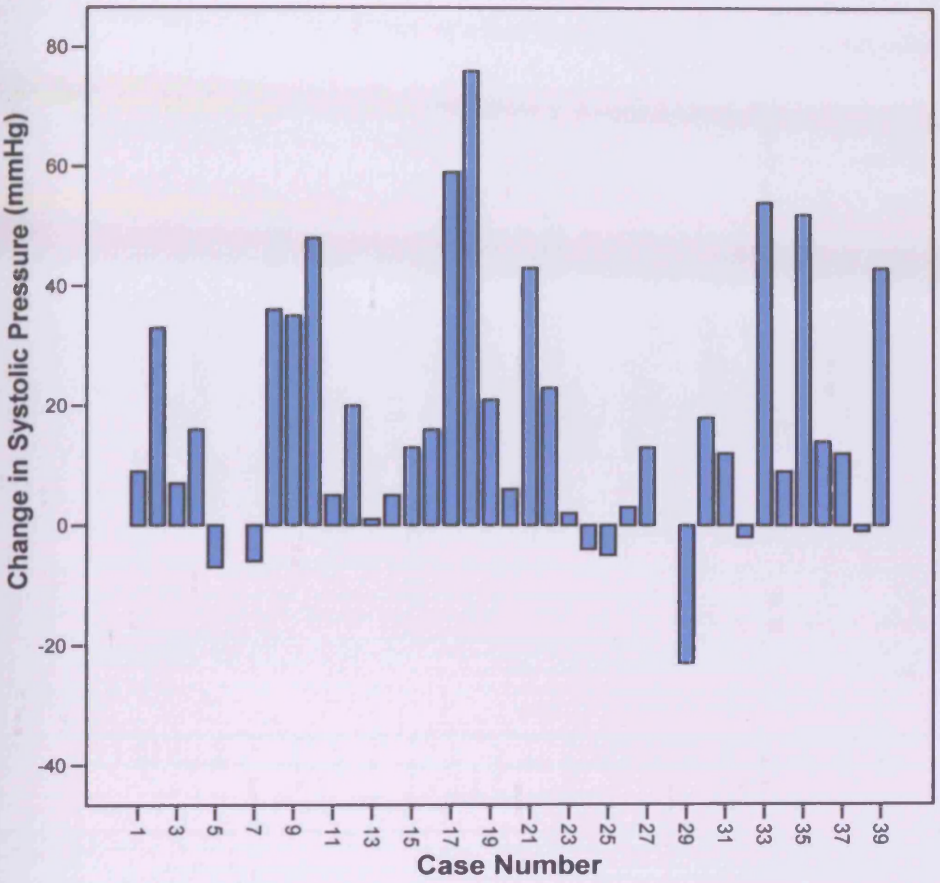


Figure 45: Individual Changes in Diastolic Blood Pressure from study start to end

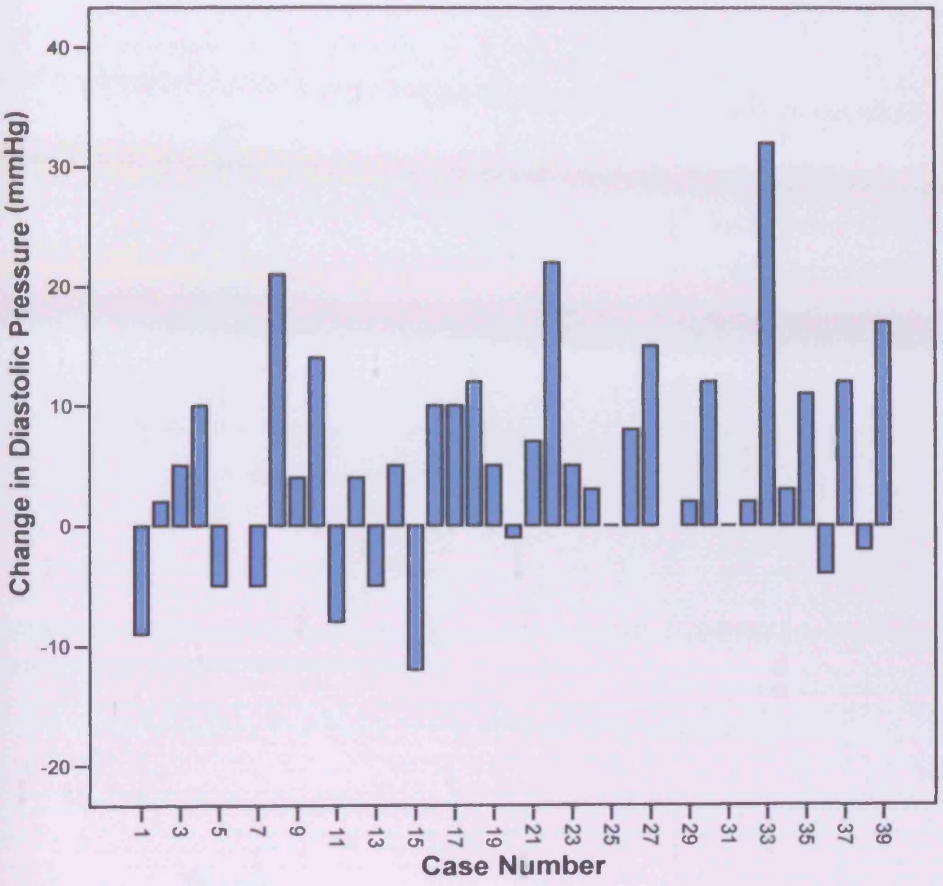


Figure 46a: Frequency Chart of Mean Arterial Pressure at study start: Patients at target at study start

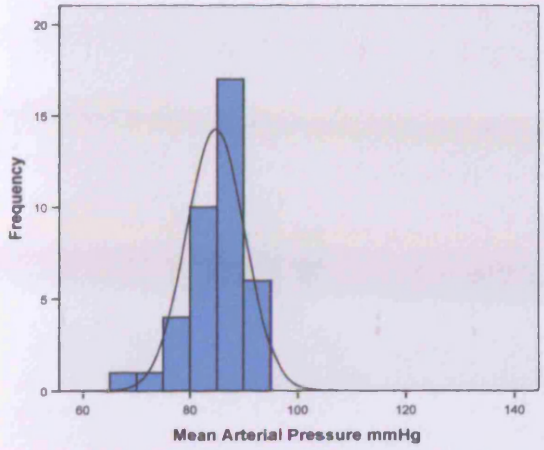


Figure 46b: Frequency Chart of Mean Arterial Pressure at study end: Patients at target at study start

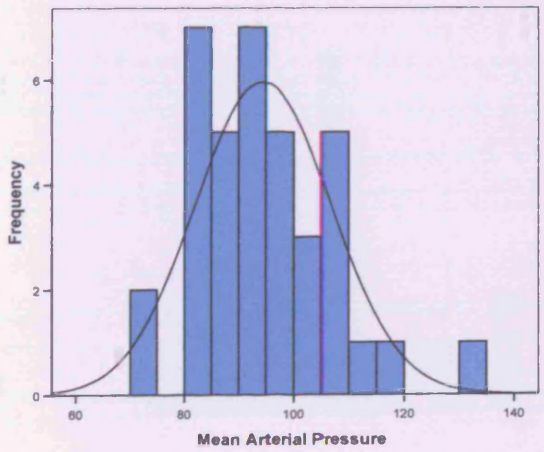


Figure 47a: Frequency Chart of Pulse Pressure at study start: Patients at target at study start

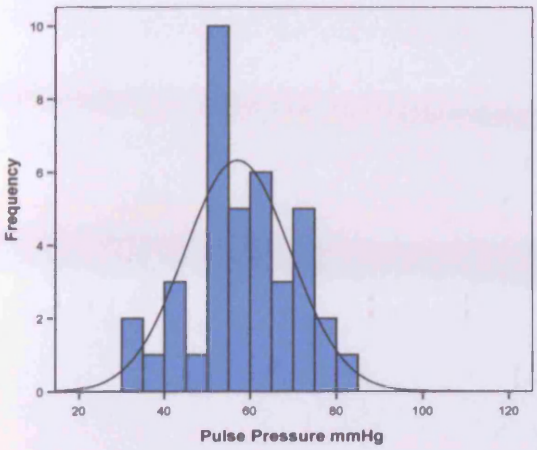


Figure 47b: Frequency Chart of Pulse Pressure at study end: Patients at target at study start

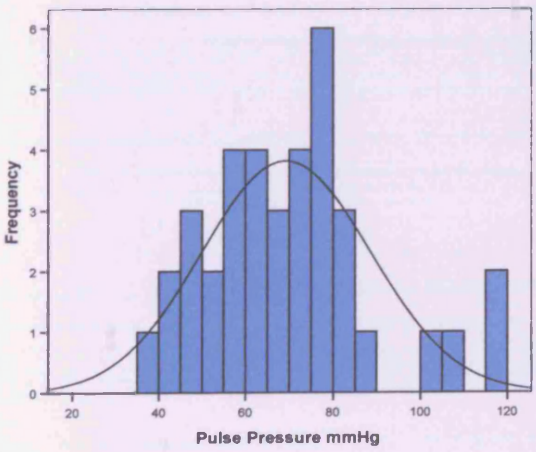


Figure 48: Mean Arterial Pressure at study start and end: Patients at target at study start

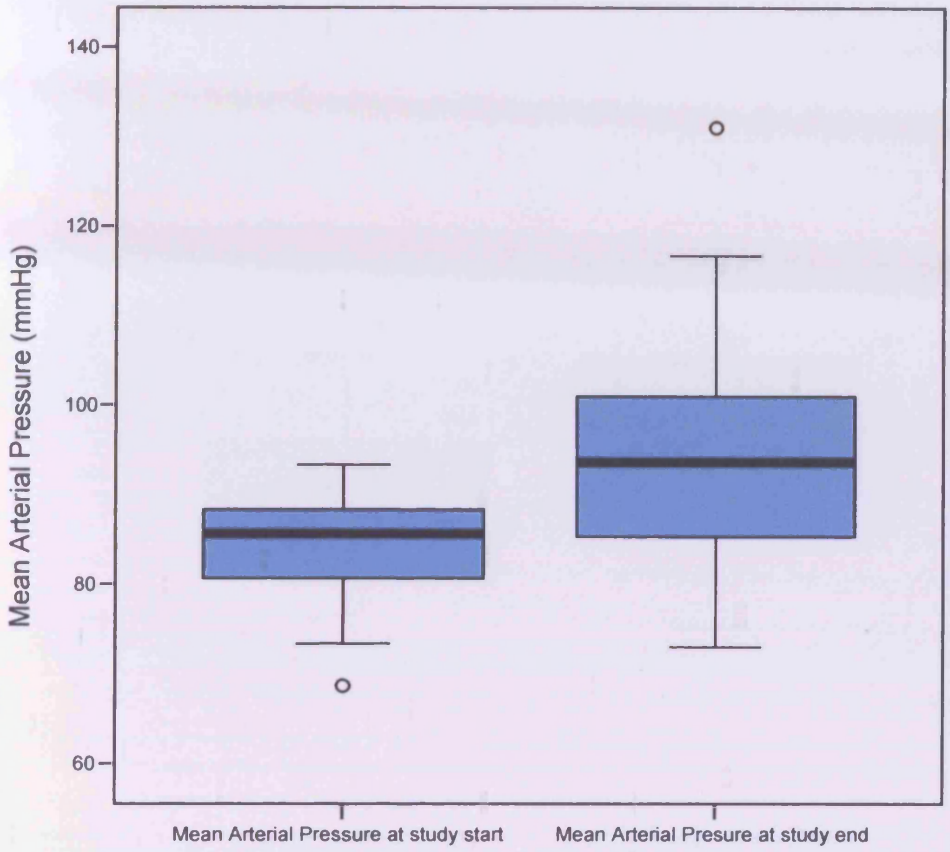
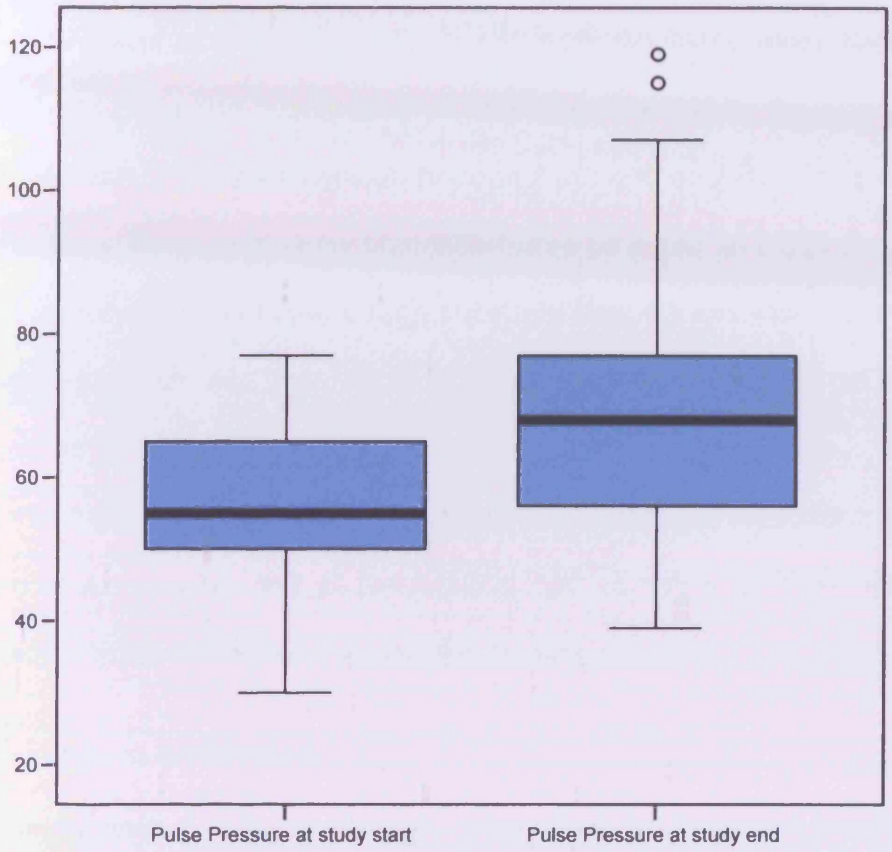


Figure 49: Pulse Pressure at study start and end: Patients at target at study start



4.4 Use of ACE inhibitors and Angiotensin Receptor Blockers

Of the total population in the study 155 (69.8%) were prescribed either an ACEi or Angiotensin Receptor Blocker (ARB) at the start of the study. An additional 18 patients of the 67 patients not receiving these medications at study start had been prescribed either of these medications by the end of the study. In addition, 2 patients were on both an ACEi and an ARB. Thus by the end of the study 78% of the study population were on either an ACEi or ARB.

In the group not at blood pressure target at study start, 53 individuals were not prescribed either an ACEi or ARB at study start and 35 had not been prescribed either by study end.

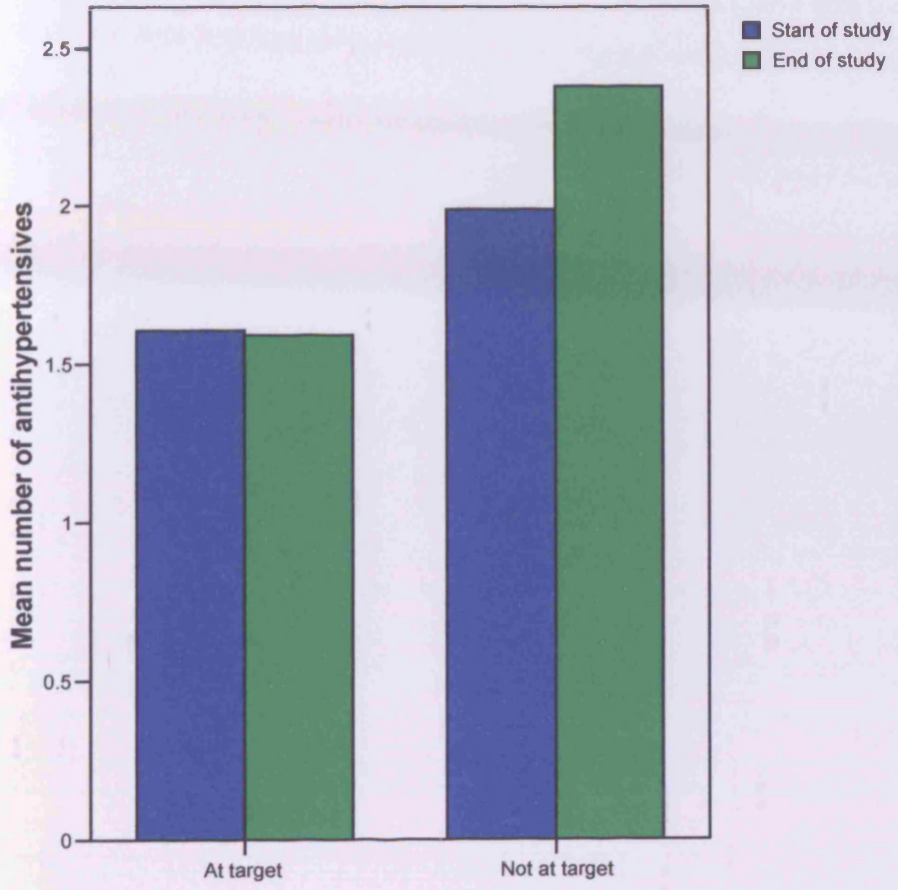
Fourteen (14) patients at target for blood pressure were not prescribed either and ACEi or AR Blocker and as the patients had no follow up there was no opportunity to make changes in prescribed therapy.

Antihypertensive medication

The mean number of antihypertensives prescribed for the whole population rose from a level of 1.87 at study start to 2.14 at study end and was statistically significant ($p<0.01$) and is illustrated in Figure 50.

The increase in the total group was found in the patients not at target for blood pressure at study start, where the mean number of antihypertensive agents prescribed per patient rose from 1.86 to 2.28 ($p<0.001$) whilst in the group at target, the mean number prescribed fell from 1.95 to 1.74, although this did notreach statistical significance ($p=0.221$).

Figure 50: Mean number of antihypertensives at start and end of study for those at, and not at target



There were a total of 467 treatment interventions made during the study. Of these, 256 were made in the clinic at the time of patient review. A significant number of treatment interventions (211 out of 467) were therefore made by the Primary Care Team, following proactive interaction with the Clinical Nurse Specialist.

4.5 Discussion

Type II diabetes is a major public health problem and with the projected increase in the number of patients with type II diabetes set to reach 300 million by the year 2025, the need for strategies to slow the progression of diabetic nephropathy is paramount . Given this increase in patient numbers there is a necessity for robust management strategies to ensure that the progressive complications of this debilitating disease are minimised. In order to delay the onset and progression of diabetic nephropathy, early detection and effective treatment is essential. This study has utilised a nurse led algorithm driven approach to improve delivery of patient care. The nurse was specifically able to interact with and engage the Primary Care Team in the process of blood pressure control to ensure that patients were not missed or lost to follow up.

The strategies that have shown the most benefit to patients with diabetic nephropathy are the control of hypertension and the use of angiotensin blockade. In the Pima Indians, pre-diabetic blood pressure was shown to predict urinary albumin excretion after the onset of type II diabetes [16]. Up to 70% of patients with type II diabetes have hypertension before the onset of persistent proteinuria with a correlation between the severity of hypertension and the subsequent development of proteinuric renal disease [16]. There is now clear evidence that successful treatment of hypertension in diabetic patients not only reduces the microvascular complications, such as nephropathy but also the macrovascular events frequently seen in this patient group [16], [36] [109]. It has also emerged that blockade of the renin

angiotensin system has benefit over and above that of lowering blood pressure in diabetic patients with microalbuminuria [36], [110, 111]. More recently evidence suggests that Angiotensin Converting Enzyme inhibitors may also prevent the onset on microalbuminuria in hypertensive type II diabetic patients [112]. Therefore, it is imperative that we develop strategies that not only control hypertension to current guideline levels but that there is the maximal use of ACEi/ARBs to provide the best renal/cardiovascular protection available. In the current study we were able to demonstrate an increase in the number of patients achieving target blood pressure and also an increase in the use of ACEi/ARBs.

The use of predefined treatment guidelines or algorithms has increased over recent years and they are useful tools which should enhance the ability of clinicians to improve patient management. However unless these guidelines are clear and concise their publication can be potentially detrimental. The publication of the NICE and BHS IV guidelines on the management of hypertension revealed differing approaches to the same clinical problem leaving clinicians unclear as to the most appropriate management and the patient with suboptimal care.

The use of an algorithm to specify drug sequencing allows the safe stepwise approach to blood pressure control by utilising the synergistic mechanism of action of the drugs on offer, rather than the traditional management of maximising dosage followed by medication switches to improve blood pressure control. In this study, the algorithm developed relied on the timely initiation of angiotensin modifying drugs and then the addition of medication to complement both the drugs already prescribed and patient comorbidity.

Publication of guidelines alone will not deliver an improvement in patient care unless they are accompanied by an implementation strategy which takes into account the numerous interfaces that exist in patient management which are potential weaknesses in ensuring success. In particular, the number of diabetic patients not achieving target for blood pressure or renal referral increased after the publication of the SIGN guidelines for diabetic nephropathy in 1997 [86]. The use of a nurse with a specific remit to implement the algorithm for control of hypertension was designed to try and tackle this issue. With the recent publication of the BHS IV and NICE guidelines and the publicity associated with the premature closure of the ASCOT trial may have further undermined the delivery of successful antihypertensive treatment.

Over recent years there have been calls to improve the management of chronic disease. This is a consequence of the fact that chronic disease, as a whole, is now the leading cause of death and disability on a world-wide scale. World Health Organisation figures now suggest that chronic disease including diabetes and obesity account for 59% of the 57 million deaths annually and 46% of the global disease burden [113]. Developing strategies to overcome this burden to the healthcare system needs innovation and thought to maximise the potential improvement for patients. There is now evidence that closer links between primary and secondary care improves the health care not only of individual patients but also for populations of patients [114, 115] [116] . In this study we have tried to improve those links with the help of a nurse led care pathway that allows feedback to and from a secondary care setting into

the patients own local health care setting. From our data 45% of the treatment changes were made in direct partnership with Primary Care and they were involved in monitoring and reporting blood pressure in all of the patients.

The British Medical Journal reported that nurse led programmes from a primary and secondary care setting were analysed for cost [117] [118] . The primary care nurse led secondary prevention of coronary heart disease was felt to be cost effective whereas the secondary care evaluation of nurse led intermediate care in the acute setting was found to be more expensive than standard care. Criticism can be made of the methods in the second study but closer inspection suggests that despite incurring higher cost initially there may be health benefit gained in the longer term. Our study bridges the gap between these 2 studies taking the best of each to deliver a service with a partnership between primary and secondary care.

Of some concern are those patients that were found to be at target for blood pressure at study entry and were then consigned to standard follow up. Blood Pressure in this group increased over the course of the study and this demonstrates it is important not to become complacent with regard to this group and that the current standard follow up may not be adequate. Treatment strategies need to be arranged to monitor these patients and the cost effectiveness of increased attendance at OPD balanced against the earlier intervention. There was no difference in number of antihypertensive medications between the start and end of the study for this group, but in addition, this was a missed opportunity to increase ACEi/AR Blocker use.

Clearly establishing a programme that enables patients with type II diabetes to be screened and treated effectively with the current level of resource will need more thought. Structuring such a programme will need cooperation between primary and secondary care to provide the best value for money and reach the widest possible number of patients.

Chapter 5

Investigation of Anaemia in a selected Cohort of Patients with Type II Diabetes Mellitus

5.1 Introduction

Although the prognosis for patients with diabetic nephropathy has improved since early reports [119] [120] , there remains an excess mortality of 70-100 times that of an otherwise matched population [104] . Survival on dialysis remains poor, with up to a third of patients dying within a year of starting dialysis [121]. Furthermore for patients who require renal replacement therapy, morbidity as assessed by hospitalization is 2-3 times greater than for non-diabetic patients with end stage renal failure . This excess of both morbidity and mortality in part relates to the high incidence of cardiovascular disease in this patient group. The identification of mechanisms which underlie modifiable factors that may prevent or slow progression or improve patient survival in diabetic nephropathy has, therefore, become increasingly important and implementation of strategies which address these issues has been outlined in the previous chapters of this thesis.

Patients presenting with diabetic nephropathy commonly have a greater degree of anaemia, for the degree of renal impairment, than those presenting with other causes of renal failure and anaemia develops earlier than in patients with renal impairment from other causes [122] [123]. Recent studies have identified anaemia as a risk factor for the need for renal replacement therapy in diabetes [124] and also that a lower haemoglobin is significantly associated with a more rapid decline in Glomerular Filtration Rate (GFR) [125]. Furthermore, treating anaemia early in renal failure has been demonstrated to slow the rate of decline of renal function [126]. Anaemia also has a negative impact on patient survival and is considered to be an important cardiovascular risk factor associated with renal disease. A greater

understanding of the pathogenesis of the anaemia associated with diabetes and nephropathy may lead to opportunities for developing interventions to optimise outcomes in these patients.

5.2 Factors identified in the literature as having an impact on the development of anaemia in patients with Type II diabetic nephropathy

Many factors have been investigated and reported in the peer reviewed literature as having an impact and being responsible, to a greater or lesser extent, for the earlier onset of anaemia in patients with Diabetes Mellitus.

These factors include:

1) Severe symptomatic autonomic neuropathy causing efferent sympathetic denervation of the kidney and loss of appropriate Epo production

2) Damage to the renal interstitium

3) Systemic inflammation

4) Inhibition of erythropoietin release.

It has also been shown that a normochromic, normocytic anaemia can occur before evidence of renal impairment is present. In order to clarify the contribution of diabetes and nephropathy to anaemia in patients with type II DM, this study examined the haematological and haematinic parameters of diabetic patients without nephropathy. A retrospective analysis was also carried out which investigated the longitudinal changes in haematological parameters of this patient group.

5.3 Methods

Individuals were recruited from the Research Clinic of the Academic Diabetes Research Unit, Llandough Hospital, Cardiff, where patients are under long term follow up. All patients had been under follow up for a minimum of five years. Sixty two (62) patients gave written informed consent. All recruited patients had been diagnosed with Type 2 diabetes and undergo exhaustive yearly health checks, including formal isotope measurement of Glomerular Filtration Rate (GFR) and assessment of proteinuria.

Retrospective data, including Haemoglobin and GFR were collated from this patient group from the time of their diagnosis and referral to the diabetic clinic – the retrospective samples have been labelled Study Point 1 for the purposes of this study.

For this study, at annual diabetic review, a blood sample was taken to measure serum ferritin, serum Epo levels and reticulocytes in addition to routine parameters including haemoglobin, haematocrit, and GFR: The prospective samples have been labelled as Study Point 2. As part of the original protocol, it had been planned that measurement of the percentage of hypochromic red cells would be undertaken and samples were collected and frozen for this purpose. During the course of the study, replacement of the analysers used for sample analysis within the haematology department was undertaken and the new analysers could not undertake measurement of percentage hypochromia. In addition retrospective haematological results were collected from the patient records for the period prior to recruitment.

5.4 Results

5.4.1 Demographic data

Analysis of basic demographic data of the patient group revealed a median patient age of 62 years with an interquartile rage of 55 to 69 years and a 45:17 ratio of male to female patients reflecting the reported gender ratio of this disease.

Patients had a median (IQR) diabetes duration of 7 (5-11) years. No patients tested positive for neither microalbuminuria nor proteinuria at Study Point 2 or had done so in the past as reflected by review of medical records.

Summary data of patient characteristics is detailed in Table 9 below and frequency charts in Figure 51 and 52 below illustrate the patient age and duration of diabetes respectively.

5.4.2 Haematological Parameters at Study Point 1

Retrospective collation of data collected at diagnosis or Study Point 1, revealed that haemoglobin was the only haematological parameter measured and in Figure 53 a histogram with normal curve illustrates the frequency of levels found. In addition Figure 54 demonstrated levels of Glomerular Filtration Rate which was measured formally at that time.

Table 9: Demographic characteristics of Patient Group (n=62)

Age (years) at Study Point 2	62(55-69)
Diagnosis (All patients)	Type II Diabetes Mellitus
Gender (M: F)	45 (72.5%): 17(27.5%)
Diabetes duration (years)	7 (5-11)

Figure 51: Frequency chart of Age in years of patient group at Study Point 2

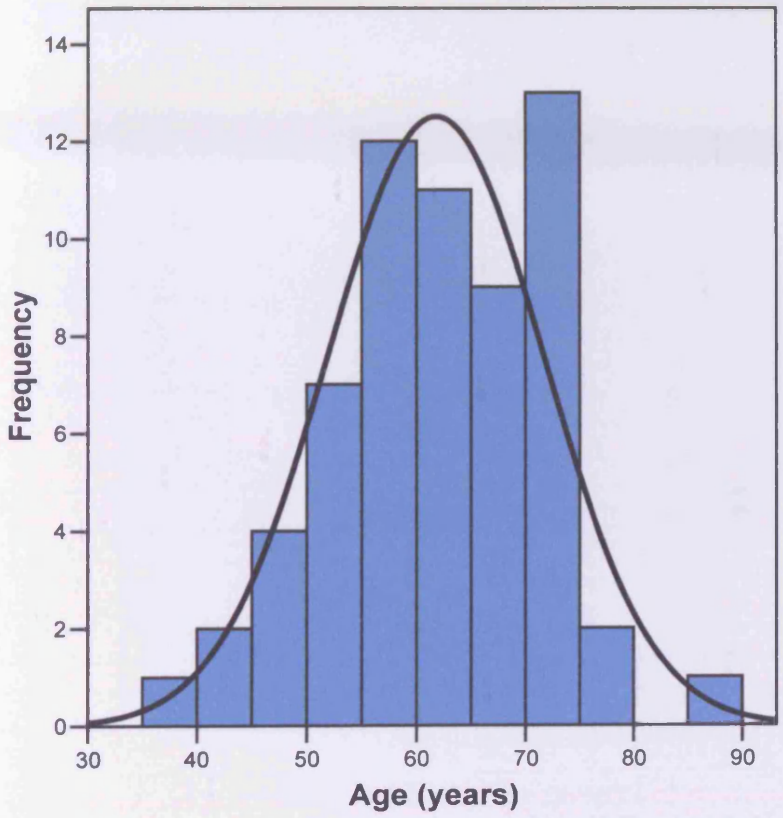


Figure 52: Frequency Chart of Diabetes duration of patient group at Study Point 2.

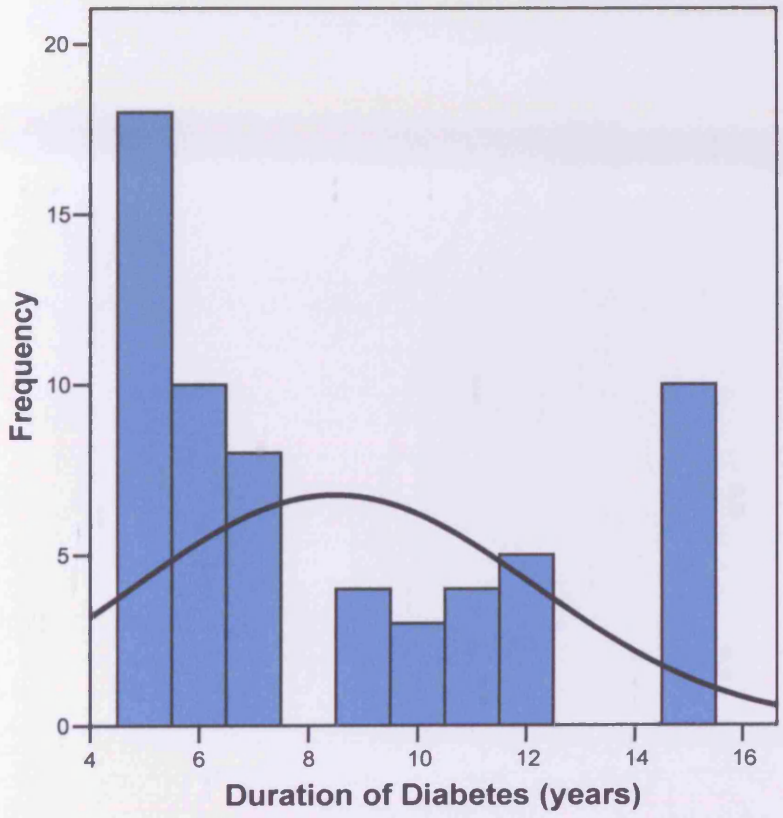


Figure 53: Frequency chart of Haemoglobin (g/dl) of patient group at presentation - Study Point 1

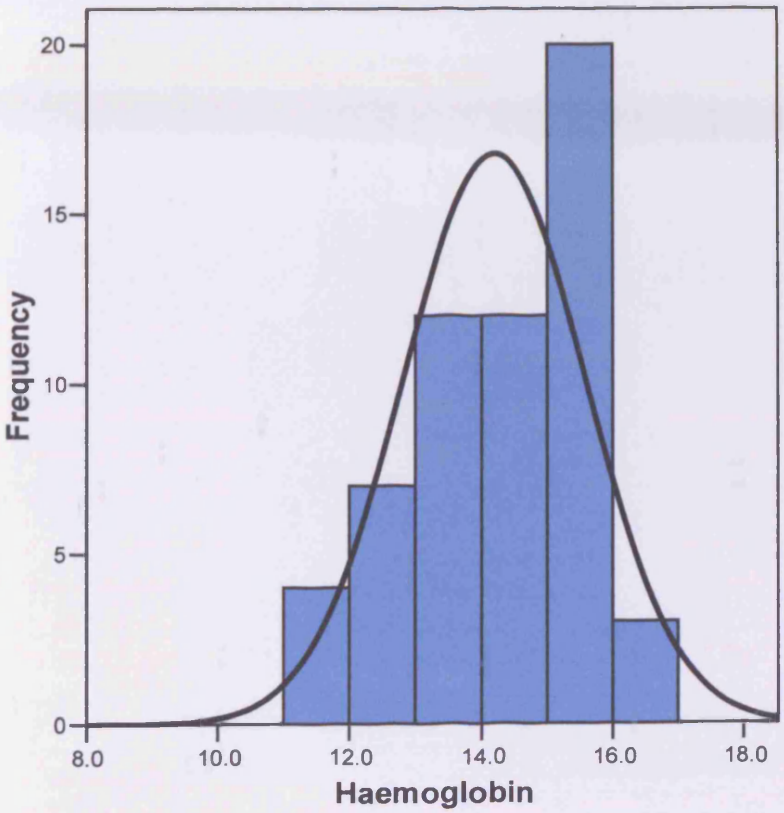
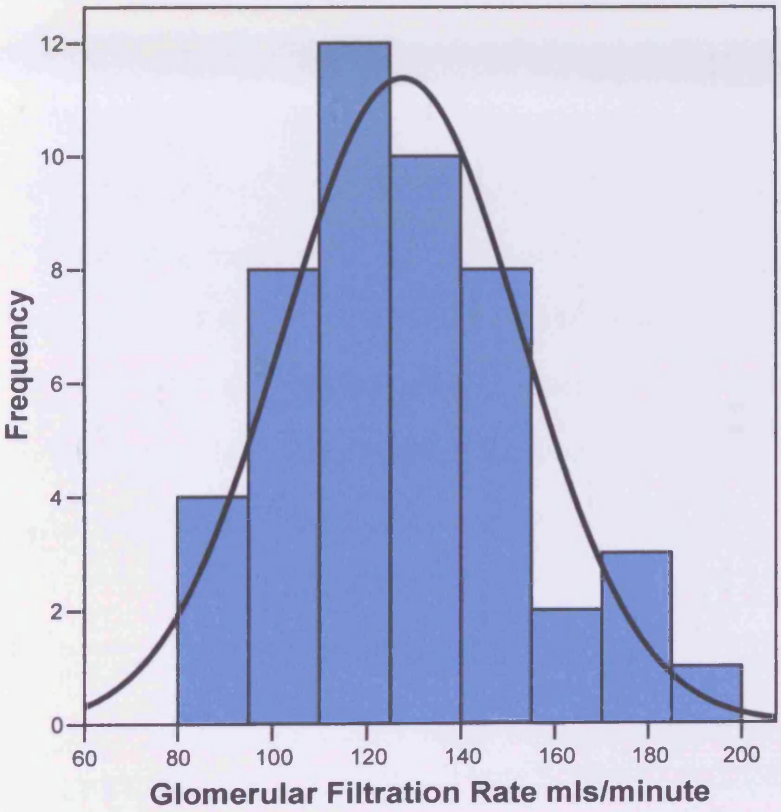


Figure 54: Frequency chart of Glomerular Filtration Rate (ml/min) of patient group at presentation - Study Point 1



5.4.3 Comparison of haemoglobin and glomerular filtration rate levels at Study Point 1 and Study Point 2.

Although only a small number of the patient group had anaemia as defined by normal values, the retrospective analysis of individual patients over time revealed a sustained although small decrease in haemoglobin from initial presentation (Figure 55) and analysis of individual changes in haemoglobin over time indicates that 36 of the 62 individuals (59%) had sustained a drop in haemoglobin (Figure 56).

Statistical analysis of this non parametric data using Wilcoxon's Rank Signed test revealed a statistically significant drop ($p=0.003$) in haemoglobin from presentation to the time of study and a similar statistically significant drop in GFR, (Figure 57) from presentation to study ($p<0.001$), reflecting a reversion from the historically described 'hyperfiltrative' state to a level of 'normal 'filtration which is part of the natural history of diabetes.

Figure 55: Haemoglobin (g/dl) of patient group at presentation with diagnosis of diabetes and at time of study

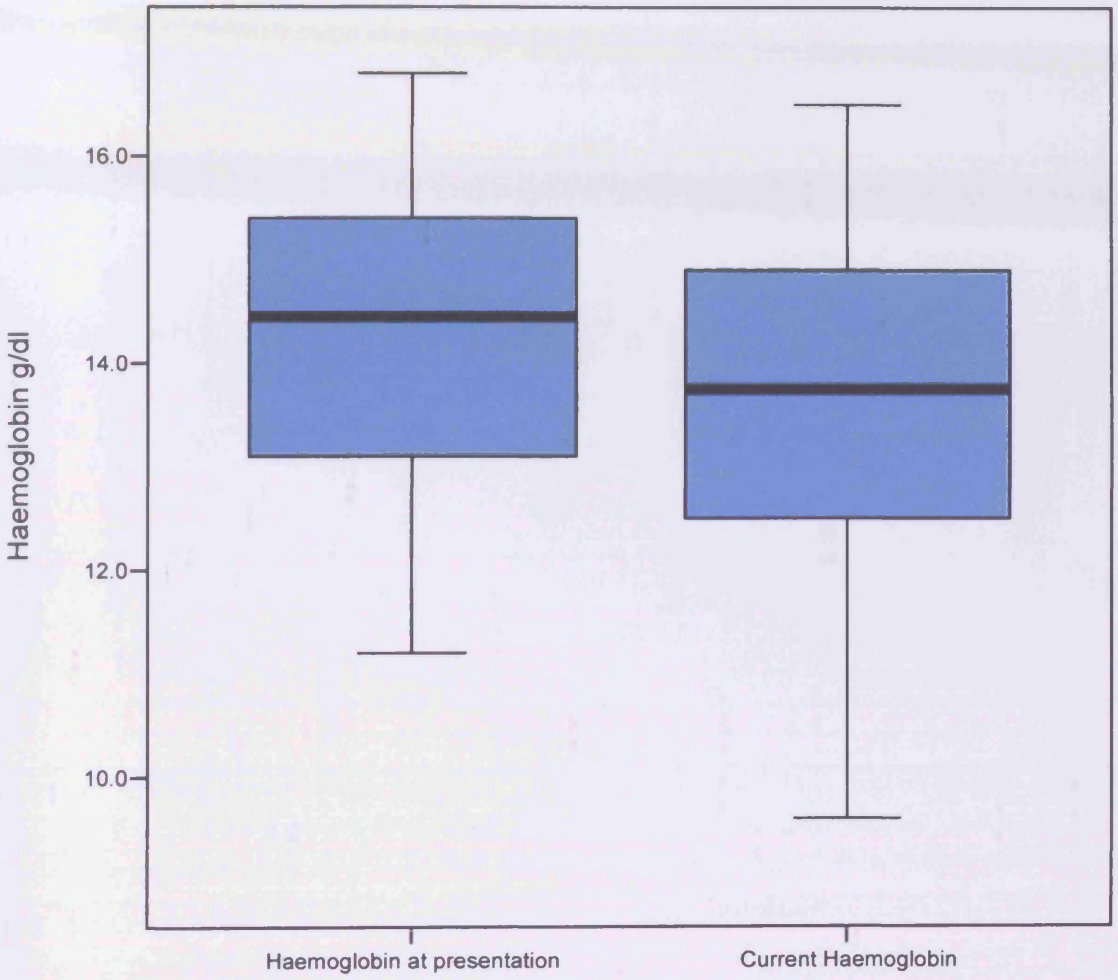


Figure 56: Bar Chart of changes in Haemoglobin (g/dl) of individuals in patient group over time from presentation to time of study.

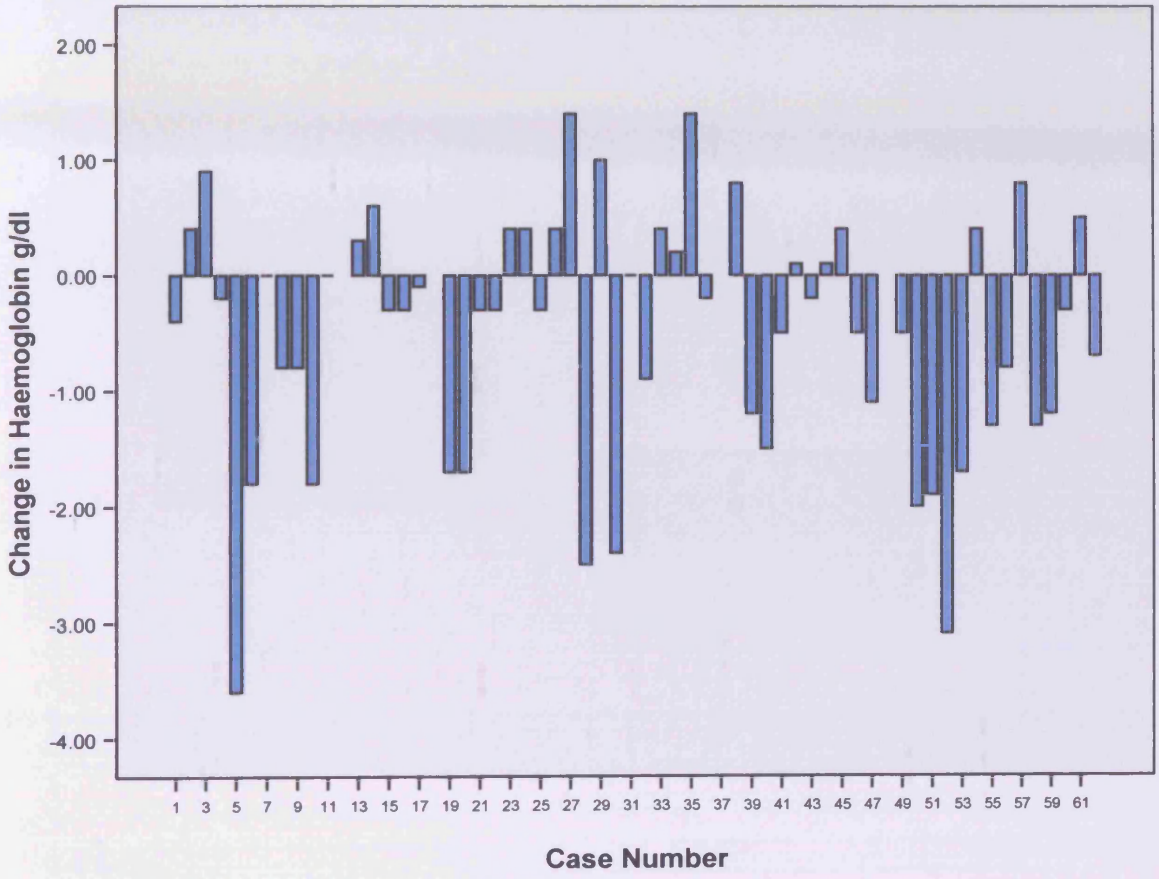
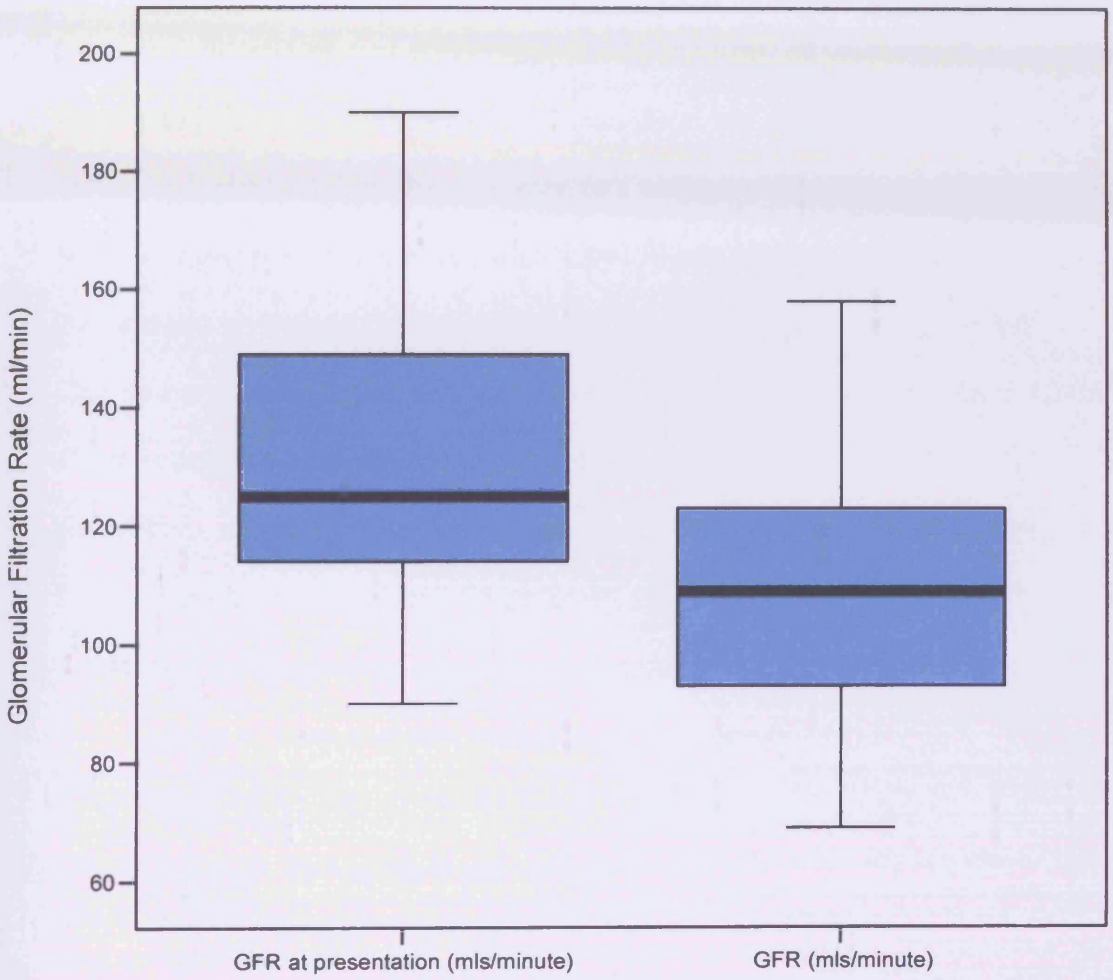


Figure 57: Glomerular Filtration Rate (ml/min) of patient group at presentation with diagnosis of diabetes and at time of study



5.4.4 Haematological and Haematinic parameters at Study Point 2

Haemoglobin levels at the time of study are detailed in the frequency chart in Figure 58 and median (IQR) levels were 13.75 (12.5 to 15.4) g/dl. Using normal ranges for male (>13g/l) and female (>11.5g/l), patients were divided into anaemic and non-anaemic groups. At the time of investigation, eight (8) Male patients out of 45 were then classified as anaemic (17.8%), while 2 female patients of 17 fell into the anaemic category (11.8%).

Median (IQR) serum erythropoietin (Epo) levels at time of study were 14(12-20) and are levels are illustrated in a frequency chart below (Figure 59).

Glomerular Filtration Rate in this patient group were median (IQR) 104(89-120)mls per minute and are illustrated in Figure 60.

Illustration of Haematocrit, Percentage reticulocytes, Reticulocytes and Ferritin levels are contained in Figures 61, 62, 63 and 64 respectively

In addition, patients were categorised into groups by haemoglobin level

- Group 1: Haemoglobin lowest to 11.5g/dl: n=6
- Group 2: 11.6 to 12.5g/dl : n=10
- Group 3: 12.6 to 13.5 g/dl: n=12
- Group 4: 13.6 to 14.5 g/dl: n=14
- Group 5: 14.6 to 15.5 g/dl: n=12
- Group 6: 15.6 and higher: n=8

Figure 58: Frequency chart of haemoglobin levels in patient group

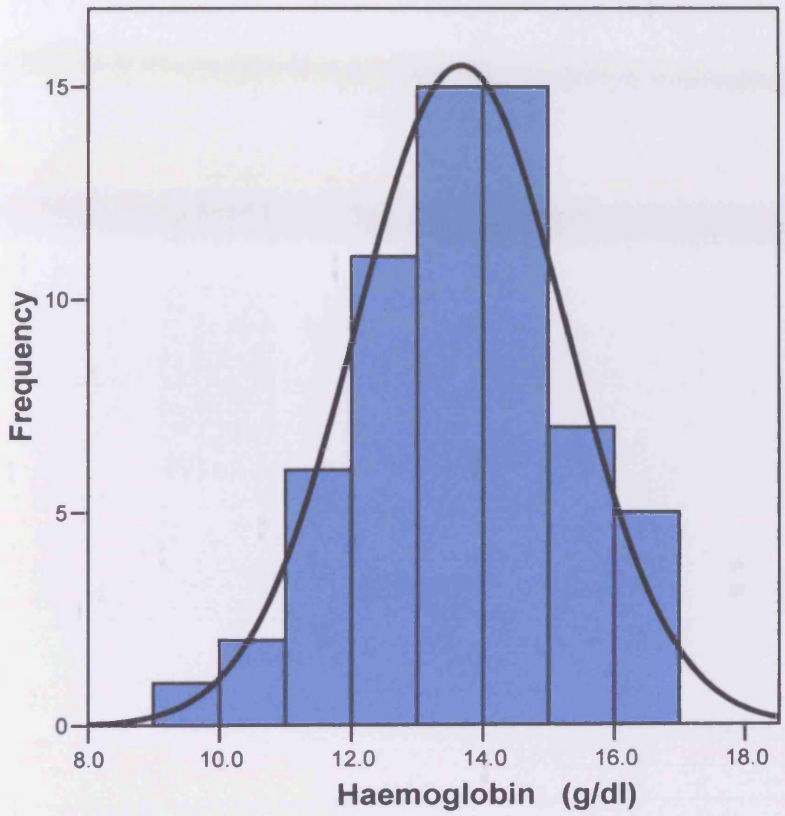
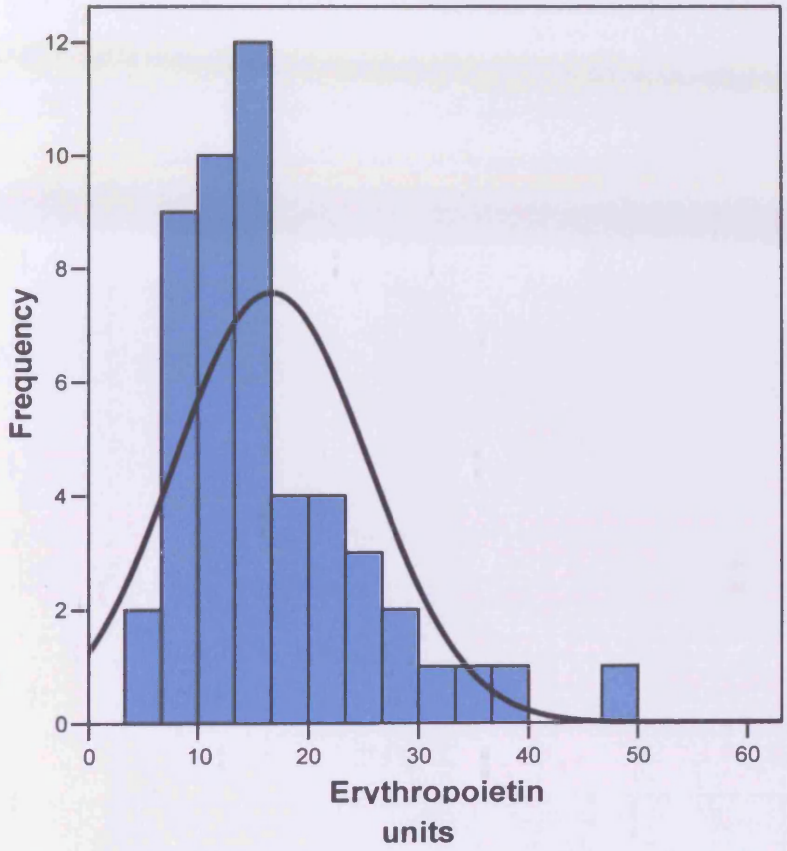
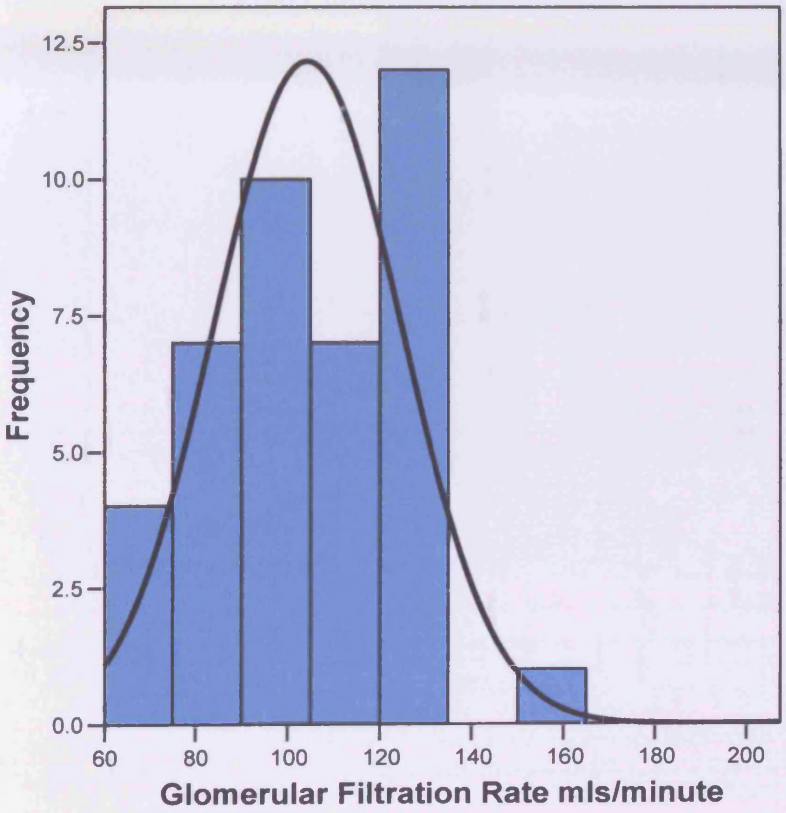


Figure 59: Frequency chart of erythropoietin levels in patient group



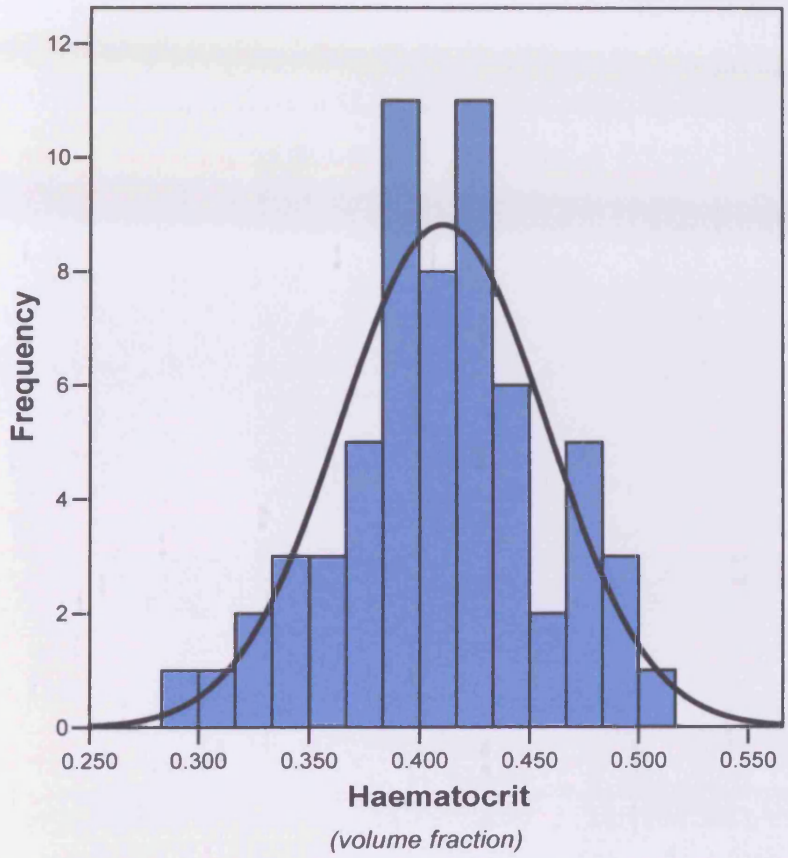
Median (IQR) 14 (12-20) units

Figure 60: Frequency chart of Glomerular Filtration Rate in total patient group n=62



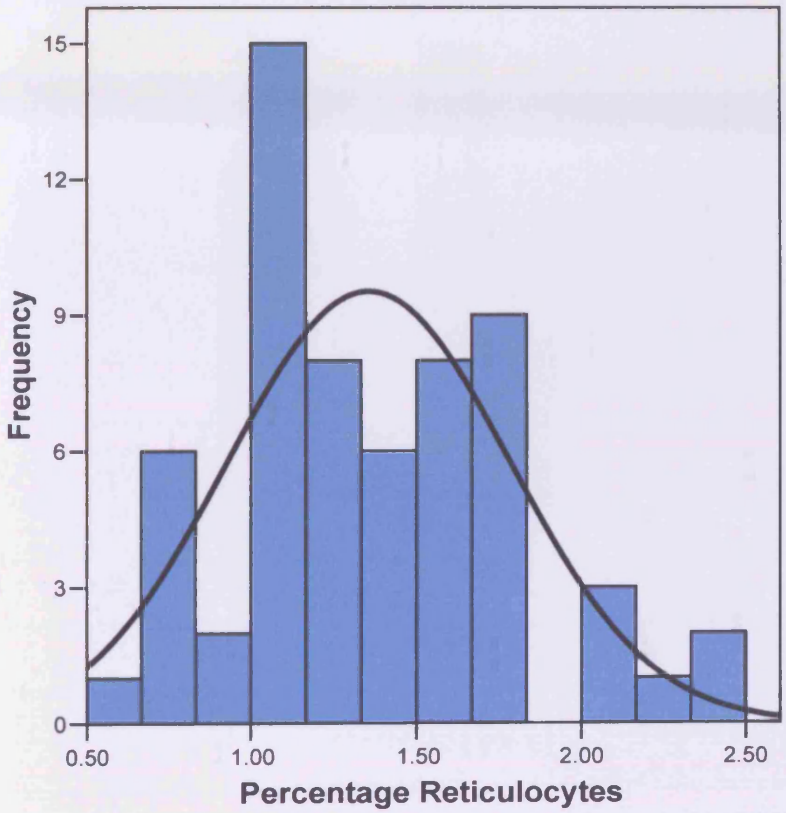
Median (IQR) 104(89 to 120) mls/minute

Figure 61: Frequency chart of haematocrit in patient group



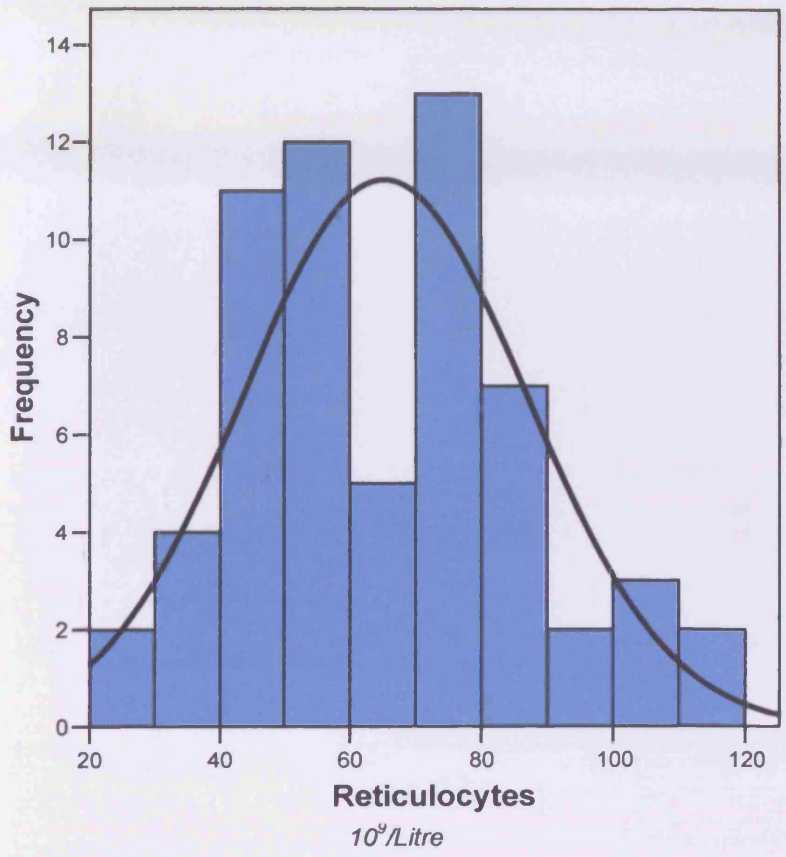
Median (IQR) 0.41 (0.38-0.44) *volume fraction*

Figure 62: Frequency chart of percentage reticulocytes in patient group (n=62)



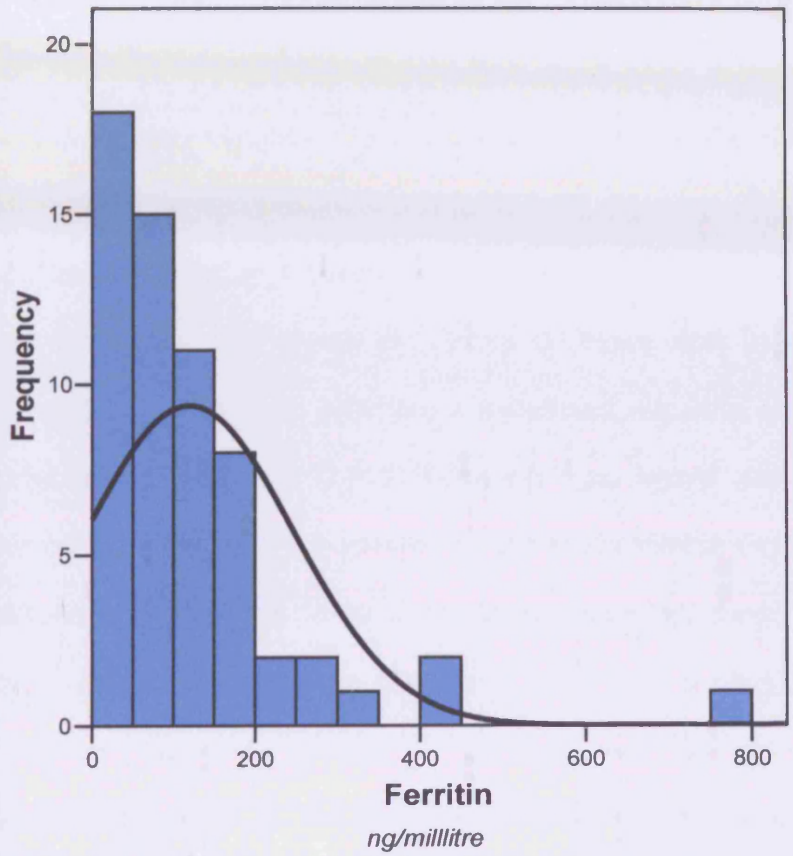
Median (IQR) 1.3 (1.0-1.6)

Figure 63: Frequency chart of reticulocytes in patient group (n=62)



Median (IQR) 64 (48 to 79)

Figure 64: Frequency chart of ferritin in patient group



Median (IQR) 93 (44 to 151)

5.4.5 Relationship between measured haematological and haematinic parameters

Serum Epo levels (units) in relation to levels of haemoglobin (Hb) at the time of follow up, are illustrated in Figure 65. These data suggest an appropriate Epo response to the fall in Hb, as Epo levels were highest in the group with the lowest haemoglobin. Statistical analysis confirms a statistically significant difference in erythropoietin levels (p=0.016), (Kruskal Wallis) with the highest Epo levels in Group 1 (those with haemoglobin levels of 11.5g/dl and less) and the lowest Epo levels in Group 6 (those with haemoglobin levels of 15.5g/dl and above). In addition, a significant negative correlation (Pearsons correlation coefficient= 0.612) between Epo levels and haemoglobin was demonstrated (p=0.01), illustrated by the scatterplot in Figure 66.

Despite the increase in erythropoietin levels in those patients with low haemoglobin, there was no commensurate, normal physiological reticulocyte response (Pearson's correlation coefficient=-0.134, ns). Neither absolute reticulocyte count (x 10^9/L) nor percentage reticulocyte count showed a statistically significant difference between the patient groups with the lowest Hb and those with the highest Hb (Figures 67 and 68), and there was no relationship between the reticulocyte count and Epo concentration (Figure 69)

To ensure that the observed changes were not the result of iron deficiency, at the time of investigation, ferritin concentration (ng/ml) was determined for all patients (Figure 70). The results demonstrated that there was no statistically significant difference in the ferritin concentration between the patients with the lowest and highest Hb, although the patients in the lowest haemoglobin grouping had clinically low ferritin levels. As these patients had not mounted a

reticulocyte response to increased erythropoietin levels it is unlikely that this relative iron deficiency was a contributor to the relative anaemia.

Figure 65: Erythropoietin levels in patients divided by haemoglobin at Study Point 2

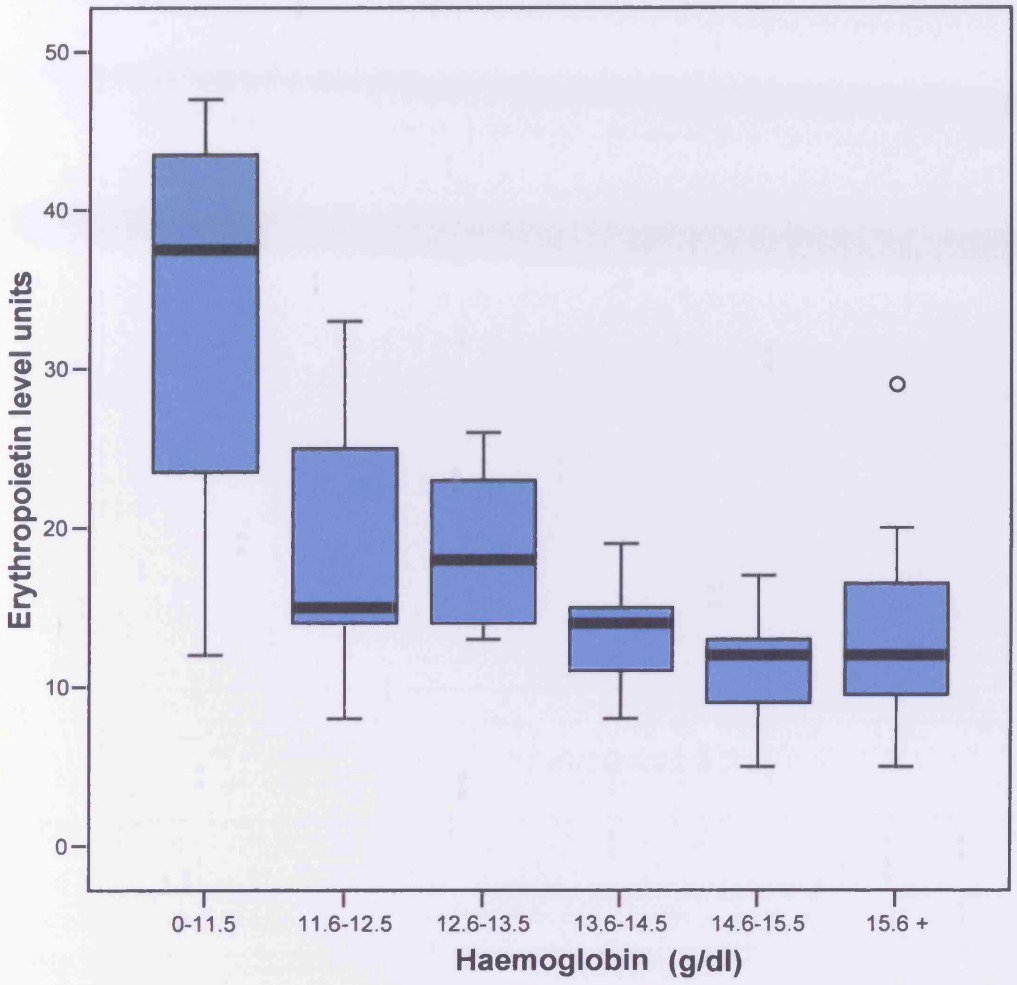


Figure 66: Scatterplot of haemoglobin and Erythropoietin levels in total patient group (n=62)

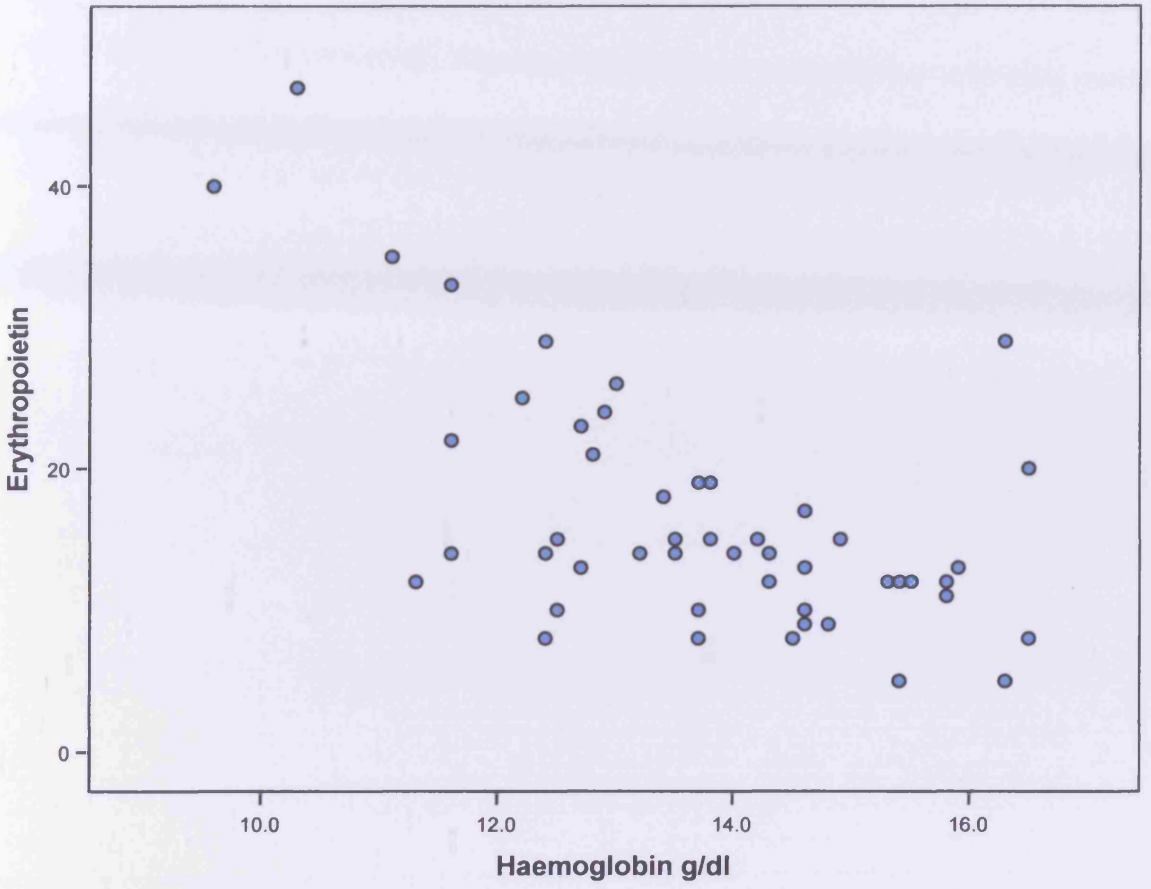


Figure 67: Reticuloctye levels in patients divided by haemoglobin at time of study

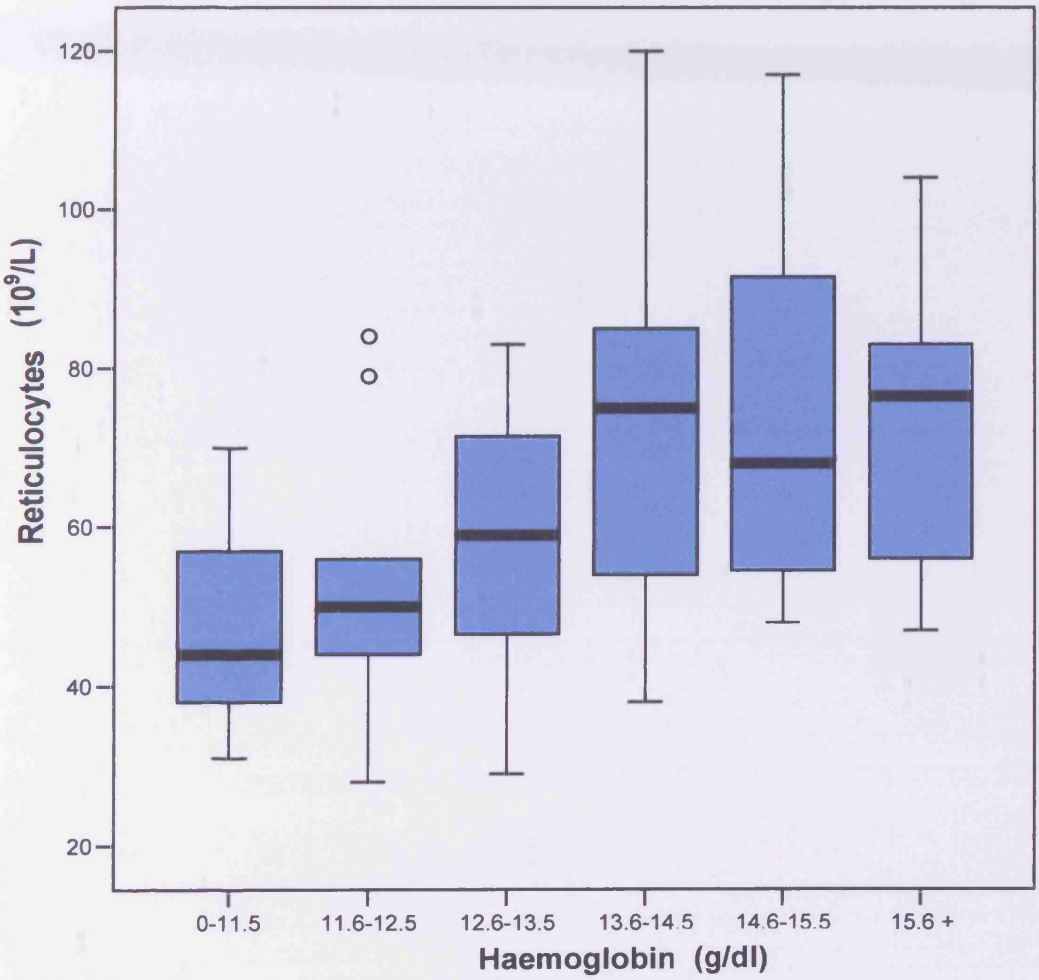


Figure 68: Percentage reticulocyte levels in patients divided by haemoglobin at time of study

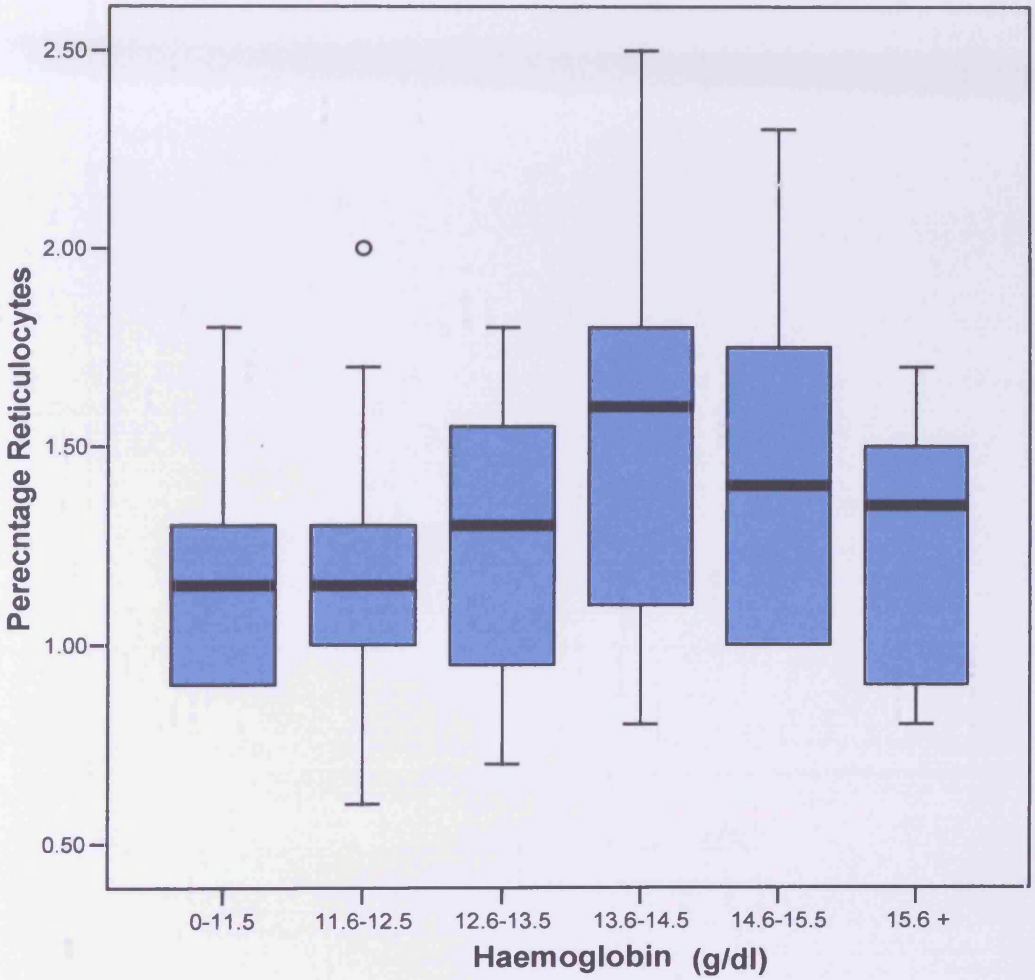


Figure 69: Scatterplot of Erythropoietin levels and reticulocytes in total patient group (n=62)

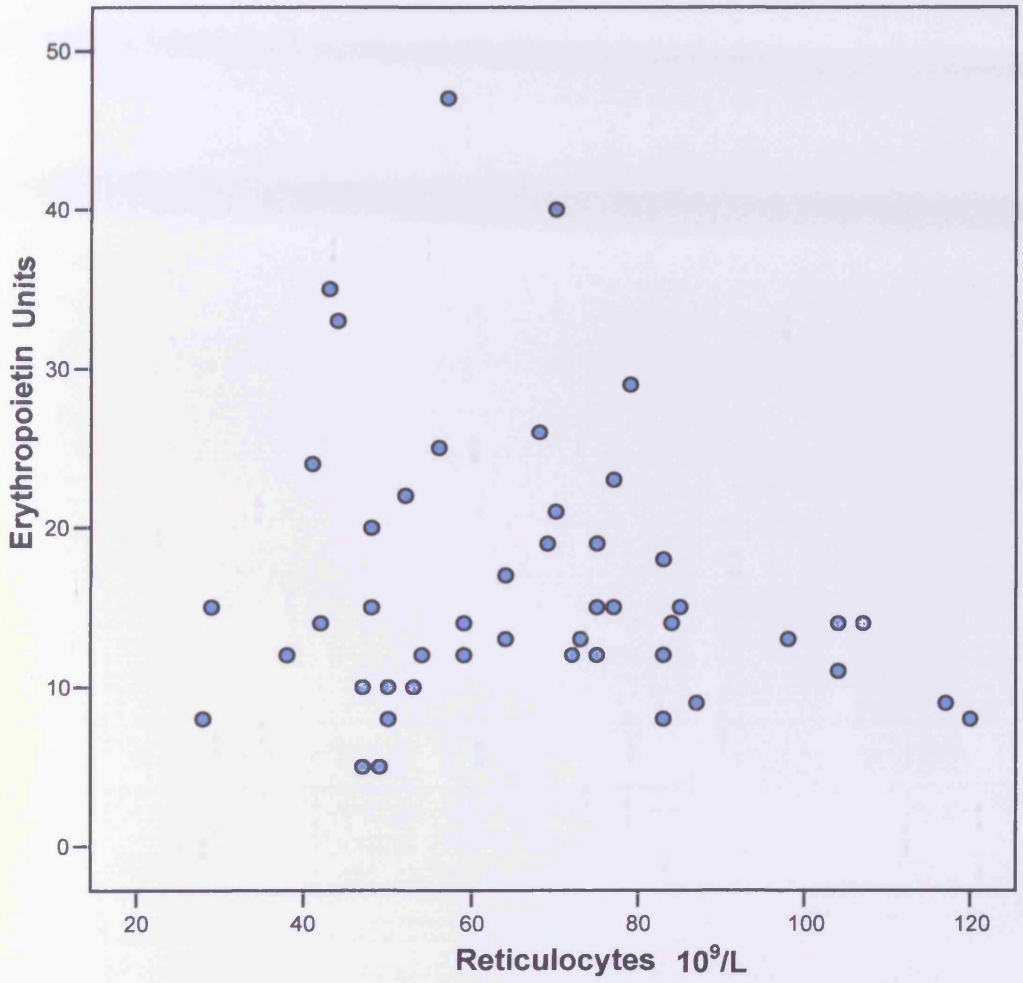
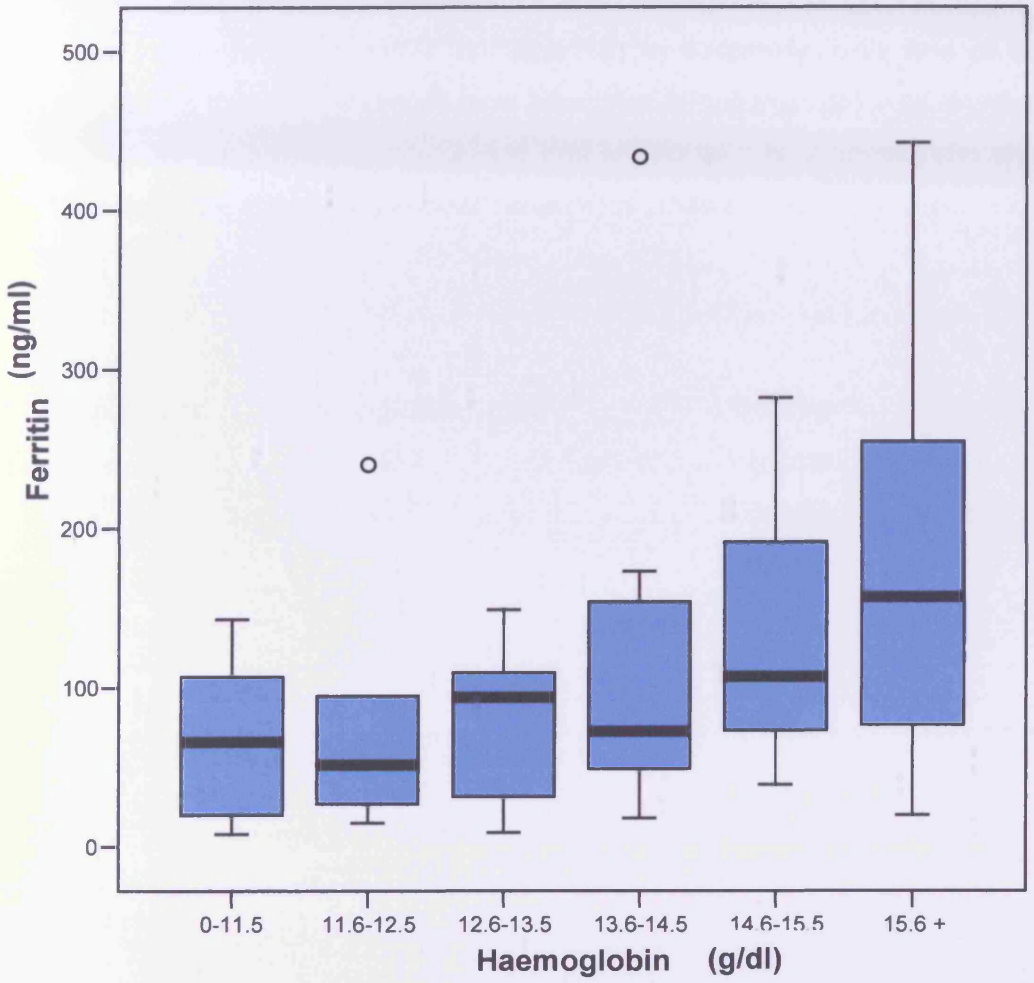


Figure 70: Ferritin levels in patients divided by haemoglobin at time of study



5.4.6 Patient Group with decreased Glomerular Filtration Rate at time of study

Of the 62 patients studied, 6 patients had a glomerular filtration rate below normal (80 mls /minute). Analysis of this patient group revealed basic characteristics described below in Table 10. In summary, only one of the patients with a lower GFR (equal to or less than 80 mls/minute) was anaemic as defined by the standard criteria and that individual was a patient identified as potentially having an additional reason for anaemia, namely rheumatoid arthritis.

Table 10

GFR (mls/min)	Haemoglobin (g/dl)	Gender	Anaemic
69	12.4	Female	No
71	12.4	Female	No
73	13.0	Male	No
74	13.7	Male	No
77	9.6	Female	Yes
80	13.7	Male	No

5.5 Discussion

Anaemia is a common complication of chronic kidney disease (CKD). It is often more severe and occurs at an earlier stage in patients with diabetic nephropathy than in patients with CKD of other causes and numerous studies have addressed the interaction between diabetes and renal failure in its pathogenesis. This anaemia associated with nephropathy results from erythropoietin deficiency, which seems to develop in patients with type 1 diabetes even at relatively "normal" levels of serum creatinine. Early erythropoietin- deficiency anaemia occurs in both Type 1 and Type 2 Diabetes Mellitus, although the prevalence may be higher in Type 1 Diabetes [127]. However, numerically most patients with erythropoietin-deficiency anaemia have Type 2 diabetes as it is a much more common disease. There is also a greater prevalence in women than men but this is not related to iron stores. In addition, erythropoietin-deficiency anaemia is associated with the presence of autonomic neuropathy in patients with diabetes. In most studies to date the predominant risk factor for the development of anaemia in a diabetic population has been found to be the presence of renal disease, manifested as impaired renal function or albuminuria [128]

Although a small number of patients in the group were overtly anaemic, it is interesting to note that 60 % had an ongoing, small but significant decrease in haemoglobin since presentation. This may be partly accounted for by the effects of age, which is known to have an effect on haemoglobin levels but the prevalence differs markedly from that of a similarly aged Caucasian population of between 2 % and 6% [6]. The levels of anaemia found in this group of type II diabetic patients are similar to the levels described in a cohort

of patients with Type I Diabetes Mellitus, in the recently published study by Thomas et al where 14% of patients were found to be anaemic [129] . It is of note however, that this study contained a significant cohort of patients with nephropathy of varying degrees, whereas the group studied within the current study had normal Glomerular Filtration Rates in the main and no microalbuminuria.

This study has attempted to unravel further our understanding of the early onset of anaemia in diabetic patients, by separating the impact of diabetes mellitus from that of nephropathy. The group of patients studied have undergone intensive follow-up in a multi-disciplinary diabetic clinic. They, by self selection to attend the research clinic are a well motivated and educated group of patients. In contrast to studies performed in patients with nephropathy, this study of diabetic patients without nephropathy shows a different picture, with the expected normal increase in Epo production in response to lowering levels of haemoglobin but without the expected normal reticulocyte response, suggesting a state of relative Epo resistance. This is in contrast to the anaemia associated with renal disease which is postulated to be a defect of "anaemia-sensing" rather than a secretory defect associated with autonomic neuropathy [130] Our data, demonstrating increased levels of Epo, suggest that diabetic patients, in the absence of renal disease, are able to mount an appropriate Epo response and are consistent with the demonstration of an appropriate response to hypoxia previously reported [122] . One of the most potent causes of suboptimal response to Epo is chronic inflammation and overt inflammation [128] associated with an increased production of cytokines such as tumour necrosis factor alpha,

interleukin-1 and interferon gamma [131] , which might suppress erythrocyte stem-cell proliferation [132] . It is interesting to speculate therefore, that overt inflammation associated with the diabetic state may contribute to Epo unresponsiveness prior to the onset of nephropathy.

Although ferritin levels are not always an accurate reflection of iron status, the majority of ferritin levels in this patient group were within the normal range and no patient had evidence of overt iron depletion. This is consistent with previous studies which failed to demonstrate iron deficiency in a mixed cohort of Type 1 and 2 diabetics [133]. These studies demonstrated elevated iron indices to be more common in patients with diabetes and suggested that excess iron may have a role in the development of diabetes.

Recent studies have highlighted an association between anaemia, the development and progression of diabetic nephropathy. There is also a high cardiovascular risk in patients with diabetic nephropathy and a clear association between anaemia and abnormal cardiac function. That development of anaemia in diabetes may pre-date any abnormality in renal function is therefore an important observation. Furthermore, understanding of the mechanism by which this occurs may provide the opportunity to develop therapeutic options which may, therefore, improve patient outcomes.

Chapter 6

The future: Managing the progression of renal disease at the interface between Primary and Secondary Care

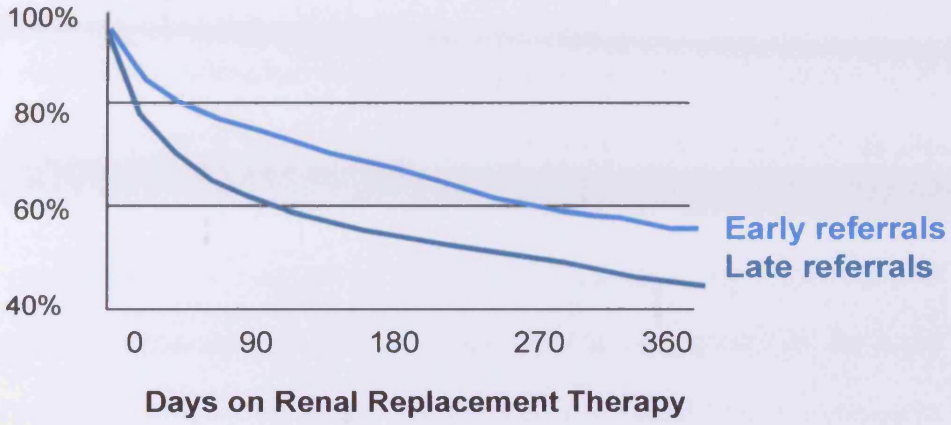
6.1 Introduction

The increasing impact of diabetes on the prevalence of chronic kidney disease has been highlighted in the previous chapters of this thesis. The focus of the work described the development and results of strategies for screening and identifying the 'at risk' diabetic population in terms of renal disease and the associated cardiovascular risk factors, accurately and efficiently. In addition, data relating to the management of a group 'at risk' for the development of chronic kidney and cardiovascular disease at the interface between primary and secondary care has been reported. Outwith the 'success' and associated resource implications the striking finding that yearly follow-up of those at target for blood pressure control and prescription of ACEi and/or Angiotensin Receptor Blockers was inadequate, serves to emphasis the size of the problem. Studies have shown that the impact of renal disease can be mitigated and that early detection, timely and appropriate referral is paramount, especially as a large proportion (between 30 and 50%) of patients with CKD die from cardiovascular disease rather than progressing to end stage renal failure [134] [135] .

Although it is outwith the scope of this thesis to consider the impact on individual of late referral to nephrology, it can be summarised by the impact on mortality of late and early referral reported by Winkelmayer et al and illustrated in Figure 71 [136] and by the length of time, up to three years, it takes for referral to a nephrologists to have an impact on levels of creatinine

World wide there is a large cohort of patients either at high risk of developing renal failure because of co-existing disease like diabetes or already with a degree of renal impairment, all of whom require ongoing, complex care in a multi-agency setting to ensure that evidence based practice is implemented and the best patient outcomes are achieved.

Figure 71: Referral patterns and patient mortality



Kaplan Meier plot of actuarial survival by timing of referral in propensity score matched population (n-2078)

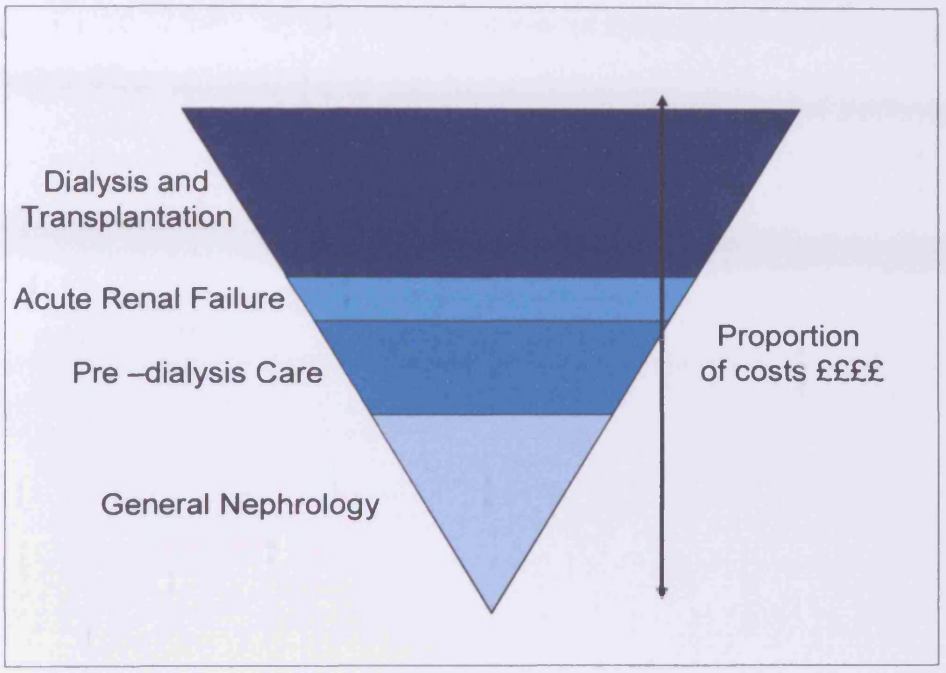
Winkelmayer WC, Owen WF, Levin R, Avorn J. A Propensity Analysis of Late Versus Early Nephrologist Referral and Mortality on Dialysis Journal of the American Society of Nephrology. 2003;14:486-92.

The previous chapters of this thesis have highlighted the potential improvement in screening and detection of diabetic nephropathy within one selected patient cohort of 200 patients. In addition, management of the blood pressure of those patients outside nationally agreed targets by a dedicated nurse specialist have shown a degree of success but the cost and resource implications are considerable. Outside the research framework, it is not practicable to undertake this type of initiative. It is not feasible nor desirable to run any service if it is dependent upon one individual and the cost of employing a nurse specialist, even if such individuals were available, for each 200 patients at risk of developing diabetic nephropathy would be prohibitive to the National Health Service. In addition, there are large cohorts of patients with diabetes who are managed exclusively in Primary Care and would therefore not be available to Secondary Care for screening.

In terms of NHS resources, diabetes is just one component of a large number of patients at risk of or in the early stages of developing renal failure from other causes. The need to reform the service to undertake the primary, secondary and tertiary prevention of renal disease is essential.

Currently the proportion of NHS income spent on renal replacement therapy, in comparison to the general nephrology budget can best be described as an inverted triangle, with the broad base representing the spending on dialysis and transplantation (Figure 72).

Figure 72


Dialysis and Transplantation
Acute Renal Failure
Pre –dialysis Care
General Nephrology
Proportion of costs ££££

In an attempt to standardise patient identification, stages of chronic kidney disease have been defined by the NKF-K/DOQI guidelines and are detailed in Table 11 below. In addition to levels of Glomerular Filtration Rate, stages must have an anatomical component - i.e. evidence of kidney disease and must also have a temporal component – i.e. have been present for at least 3 months.

These stages have been used as a basis for formulating strategies for referral and management across primary and secondary care, to deal with the large numbers of affected individuals.

Table 11: Definition and stages of Chronic Kidney Disease according to NKF-K/DOQI guidelines

Stage	Description	GFR (ml/min/1.73m^2)
--	At increased risk e.g. known diabetes or hypertension	≥ 60 (with CKD risk factors)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 or dialysis

6.2 What is the problem?

The size and scale of this problem of diagnosis and management of CKD, of which those with diabetic nephropathy comprise one of the high risk groups, is a challenge for many parts of the National Health Service especially as it comprises around 20% of the prevalent patient numbers new to renal replacement therapy [137].

As reported by Amhad et al in 2006, service planning for the care of patients with CKD is difficult, as there are no data available on patients approaching renal failure and there is no information on the facilities available to look after this patient group [138]. The authors contrast the paucity of information available for the pre RRT phase with the wealth of data available on the patient status and facility characteristics of those on RRT, where the infrastructure for collection, collation and distribution of data has been centrally funded. The authors then reported data from seventy (70) units in the United Kingdom in which they attempted to quantify the number of patients attending nephrology services. The data from twenty five units showed that the median (IQR) ratio of prevalent CKD patients to prevalent renal replacement therapy patients was 3.7(2.7-5.7) and the median (IQR) ratio of CKD Stage 4 and 5 patients /prevalent RRT patients was 0.6(0.4-1.1). The authors estimate, therefore, that UK wide there are around 140,000 CKD patients under the care of nephrologists with 23,000 of those at stage 4 or 5.

6.3 Impact of geography: Data from Wales

Estimates of patient numbers in Wales from the National Standards Framework for Renal Disease for Wales [139] are detailed below in Table 12 and identify a total CKD population of around 400,000. It should, however, be remembered that of the 150,000 patients at Stage 3, only <1.5% will progress to end stage renal disease.

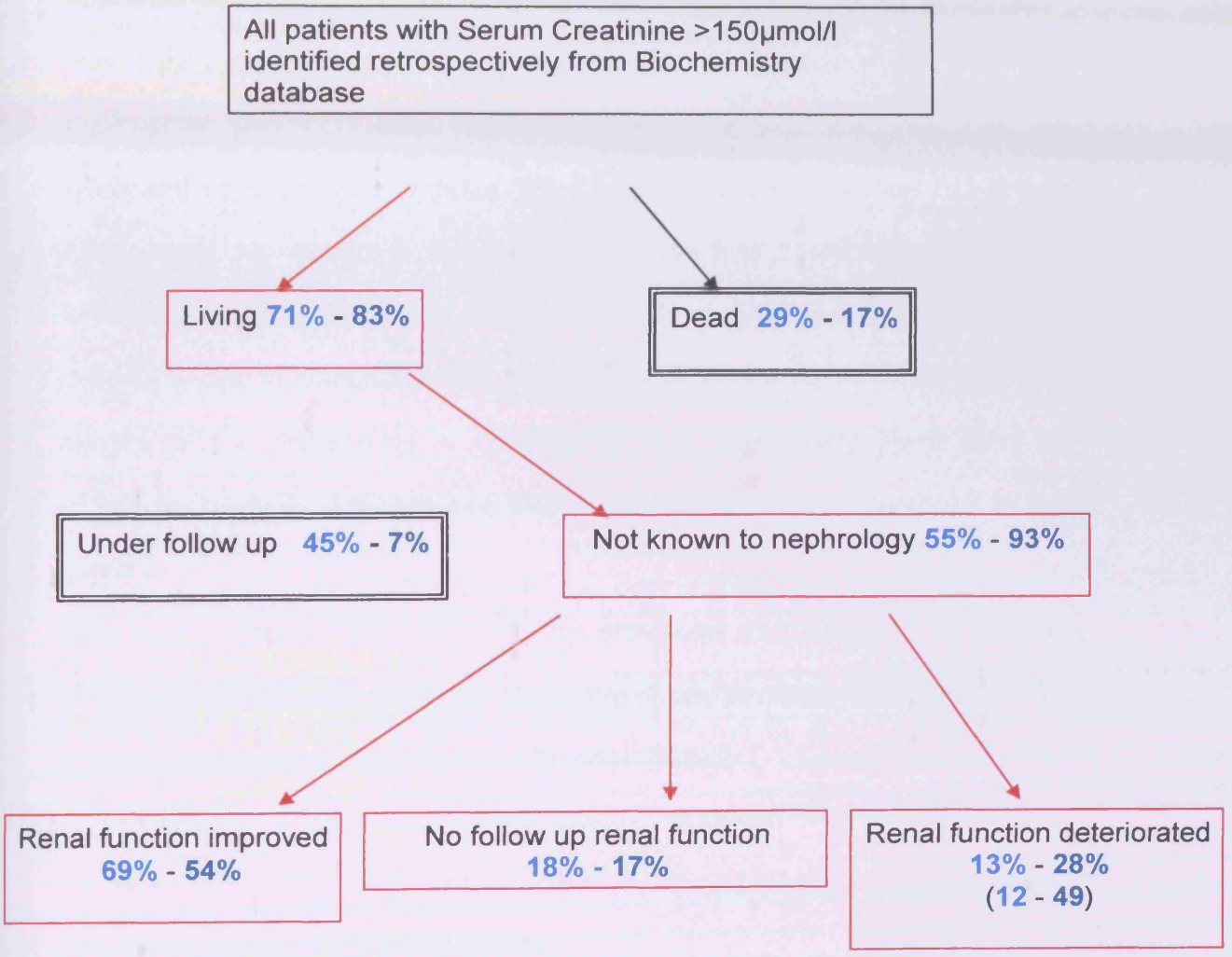
Table 12

Stage	Percentage	Number
Stage 1	4%	120,000
Stage 2	4%	120,000
Stage 3	5%	150,000
Stage 4	0.2%	4000
Stage 5	0.08%	2400

Some insight on the proportion of patients with CKD under the care of the nephrologists, in comparison with those being looked after by others (Primary Care and other medical specialities) was gained from a retrospective study by the author comparing two hospitals of similar size and catchment area, both in the same region and with similar socio-economic background. One of the two hospitals has a renal outreach clinic and a ward consultation service. Audit of two separate weeks identified approx 500 individual patients with serum creatinine greater than 150μmol/l, which were the current referral guidelines and although not providing an accurate reflection of renal status was the only

way to identify patients, given the limited information recorded by biochemistry. An algorithm detailing the differences in patient referral to nephrology between the hospital with a renal presence, in comparison with the hospital without, is shown in Figure 73 below. As can be seen from the percentages in the algorithm, of the 355 living patients, 55% from the centre with nephrology input were not known to nephrology whilst 93% of the patients from the centre without nephrology input were unknown to the nephrology service. Of the 195 patients not known to nephrology, it appears appropriate that a number of these patients were not known to nephrology, as further biochemistry results reveal a return to normal levels indicating an acute episode of renal failure. Of more concern, was the group of 106 patients who were not known to nephrology but who either had no follow up result (n=45) or had a follow up result that showed worsening renal function (n=61). This indicates that in this small sample, there were 160 patients under nephrology follow up but in addition there were 92 patients who were not under follow-up by the nephrology service but probably should have been.

Figure 73: Algorithm of referral/non referral of patients with elevated plasma creatinine



Geography and access to specialist services impacts not only upon issues surrounding referral to nephrology, but also upon the take-on rate for dialysis of patients living at some distance from renal centres. These issues are illustrated pictorially in Figure 74, taken from a study from White et al [140] . This paper highlighted that the prevalence of haemodialysis (HD) fell significantly with increasing travel time from unit and that this was not influenced by deprivation indices. Prior to the opening of a new HD unit in Aberystwyth, prevalence in the surrounding area was significantly lower than for Wales as whole but within 2 years, prevalence had risen to approximate national levels. In Haverfordwest, an area more than a 30 min drive from any current facility, prevalence is consistently and significantly lower than for Wales as a whole and has not shown the growth seen elsewhere in the country.

Data from Canada, Figure 75 [141], has previously demonstrated, in addition to a lower take-on rate, distance from nephrology services impacts upon the mortality and morbidity of patients with renal disease .

The geography of Wales means that particular solutions need to be thought out for a number of patients living in Wales, to compensate for the difficulties inherent in the geography of the area.

Figure 74: Drivetimes for centres serving Wales

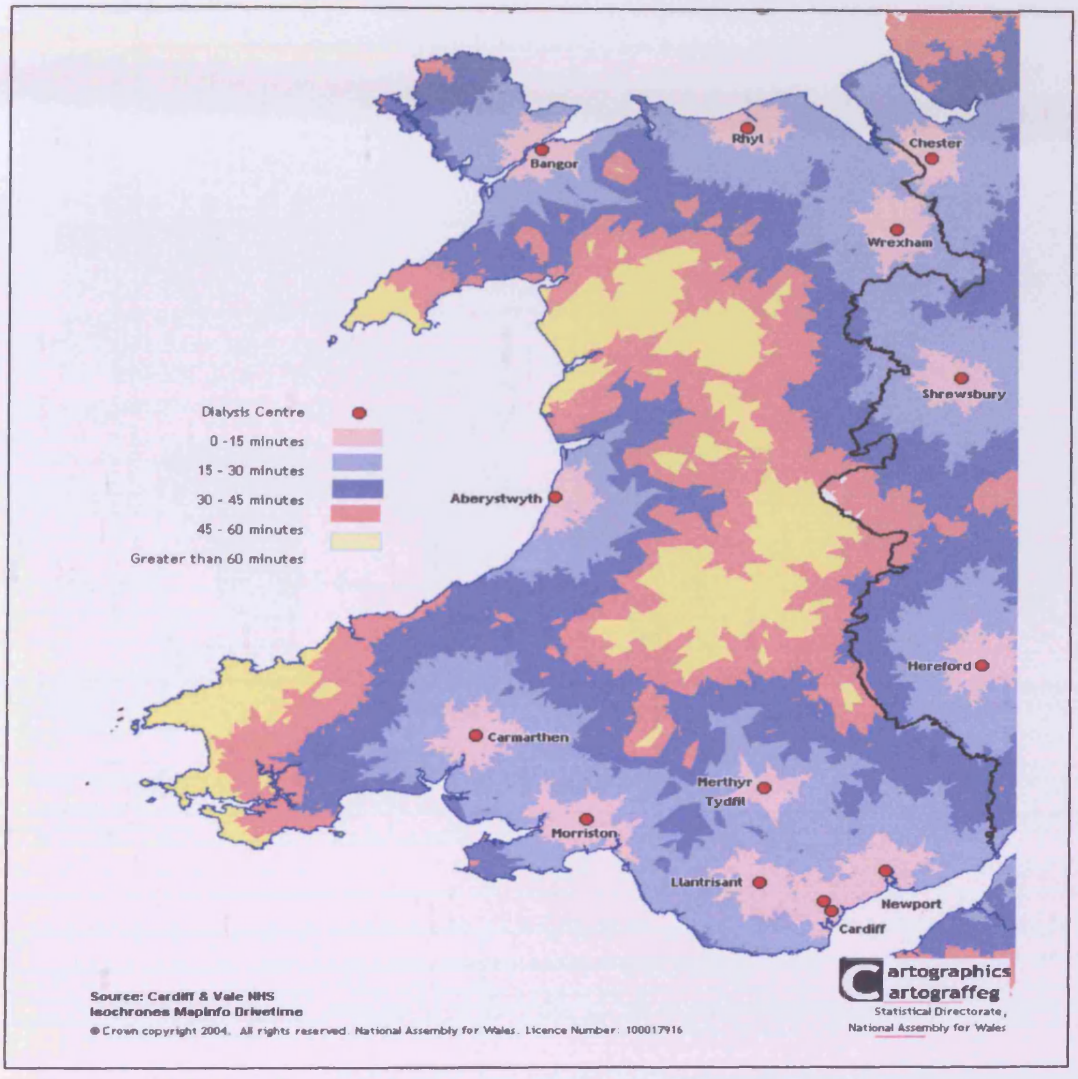
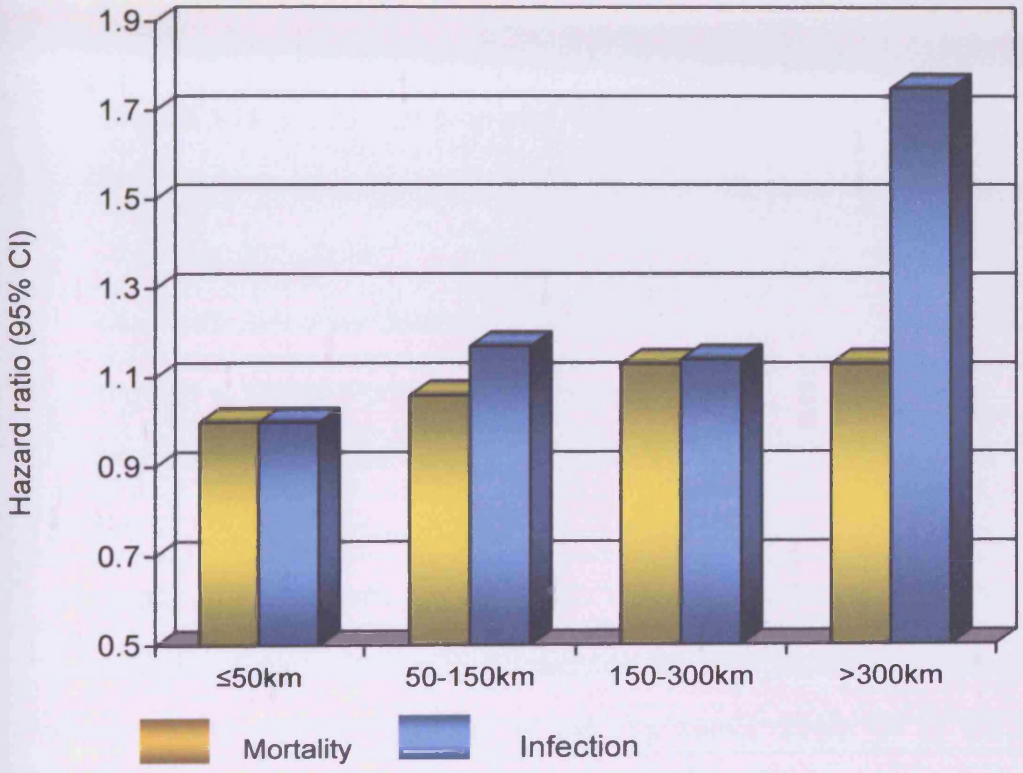


Figure 75: Proximity to nephrologists: levels of mortality and infection.



6.4 Solutions and Responses to Problems

6.4.1 National Service Framework for Renal Disease in Wales

The National Service Framework for Renal Disease in Wales [139] commissioned in 2004 and published in March 2007 comprises the following modules

Module 1: Care for Children and Young People

Module 2: Prevention of Chronic Kidney Disease and Management of Acute Renal Failure

Module 3: Effective Delivery of Dialysis

Module 4: Organ Donation and Transplantation

Module 5: Alternative Models of Care.

Module 2, the Prevention of Chronic Kidney Disease and Management of Acute Renal Failure is directly relevant to the work undertaken as part of this thesis and highlights the care of patients being cared for at the interface between Primary and Secondary care. Following the publication of a detailed 'Standards' document two main outcome measures for Module 2 scheduled for complete implementation Wales-wide by 2008 were highlighted:

- The quality of monitoring patients at risk will have been improved by implementing an agreed common method for measuring renal impairment. i.e. eGFR.

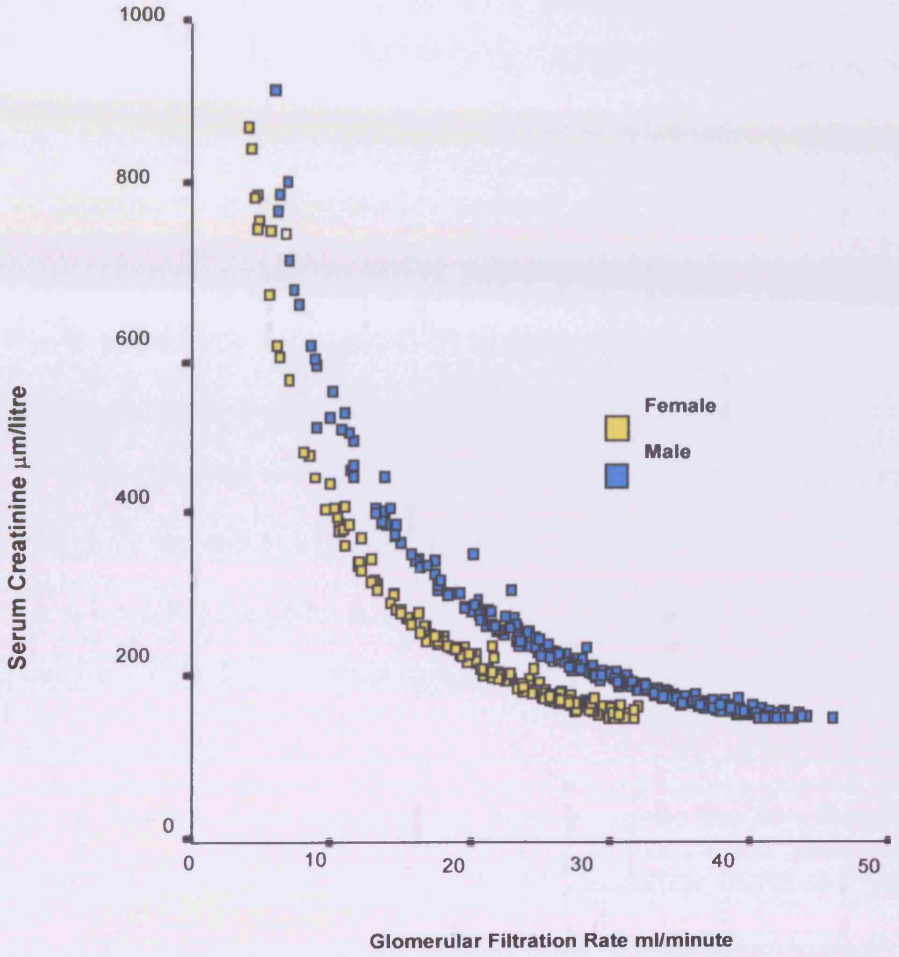
Glomerular Filtration Rate (GFR) is the most commonly used measure of kidney function. The gold standard for GFR measurement uses compounds

which are injected into the blood stream and are filtered in an unaltered state by the kidney. Traditionally compounds that can be used include those such as Inulin, the excretion of which can be measured by timed samples of blood and urine from which the excretion of Inulin can be measured. Other substances which may be used include Chromium labelled EDTA and radio contrast e.g. Iohexol. All these methods are labour intensive, expensive and have considerable resource implications in terms of staff time, finance and patient availability. This makes these methods unsuitable for use as a screening tool in a large 'at risk' population. An alternative method is to collect timed urine collections, normally over a twenty four hour period. This method is time consuming and is open to much interference as the accuracy of the totality of the collection is difficult to ascertain. GFR declines naturally with age and after 30 years GFR may decline by between 4 to 10 millilitres per minute per decade.

Because of the difficulties, costs and logistical difficulties of obtaining GFR measurement, the standard method for many years has been serum creatinine. This measurement is simple and easy to do as well as being a cheap test to undertake. Among the negatives are the fact that serum creatinine is a static measurement of a dynamic process; that although creatinine rises with a falling GFR, the relationship is not linear; serum creatinine can remain in the normal range until the GFR reaches 50%; non renal elimination is increased in CKD; may be influenced by diet; is affected by muscle mass (in particular this may have an effect in relation to age, gender and race); can be influenced by certain drugs e.g. trimethoprim.

Most experts in the field agree that the simplified and agreed standard MDRD equation which requires plasma creatinine, age, gender, race is the most accurate and simple measure of renal function in an 'at risk' population. This has been accepted as the validated method which has been used in the UK. There are alternatives methods, but all have limitations including MDRD equation. The MDRD equation has limitations which include 1) that there is the potential for interference from bilirubin, ketones and protein levels 2) that there is a limitation to its use in the healthy population who have greater muscle mass and better diet; and 3) it is of limited value in the acutely ill as this condition is rarely a 'steady state' and immobilisation, malnutrition and catabolic illness may all alter creatinine production. Although there are limitations associated with the use of the MDRD equation, its use is an improvement on the use of serum creatinine alone. The relationship between serum creatinine and eGFR result in the previously audited patient group described above is illustrated in Figure 76 below and highlights the differing eGFR results obtained from similar serum creatinine results.

Figure 76: Relationship between serum creatinine and eGFR



6.4.2 Introduction of Quality Outcomes Framework (QOF)

Renal disease has been introduced as a domain in the Quality Outcomes Framework for the first time in 2006 in Wales. The framework has four outcome measurements detailed below

CKD 1- generation of a register of patients with Stage 3, 4 or 5 Chronic Kidney Disease based on eGFR. (6 points awarded)

CKD 2 – % of patients with record of blood pressure recorded in the last 15 months (6 points awarded)

CKD 3 - % of patients with blood pressure below 140/85mmHg recorded in the last 15 months (11 points awarded)

CKD 4 - % on CKD Register prescribed an Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker (unless contraindicated) (4 points awarded)

Anecdotally, Primary Care practitioners have indicated that the majority of the information required to gain 26 out of the 27 available points from the renal outcome measures were already collected as part of other chronic disease registers, in particular cardiovascular, diabetes, hypertension or stroke.

The key change for the NHS was the fact that the collection of these data highlighted the number of patients in Wales with Stages 3-5 CKD.

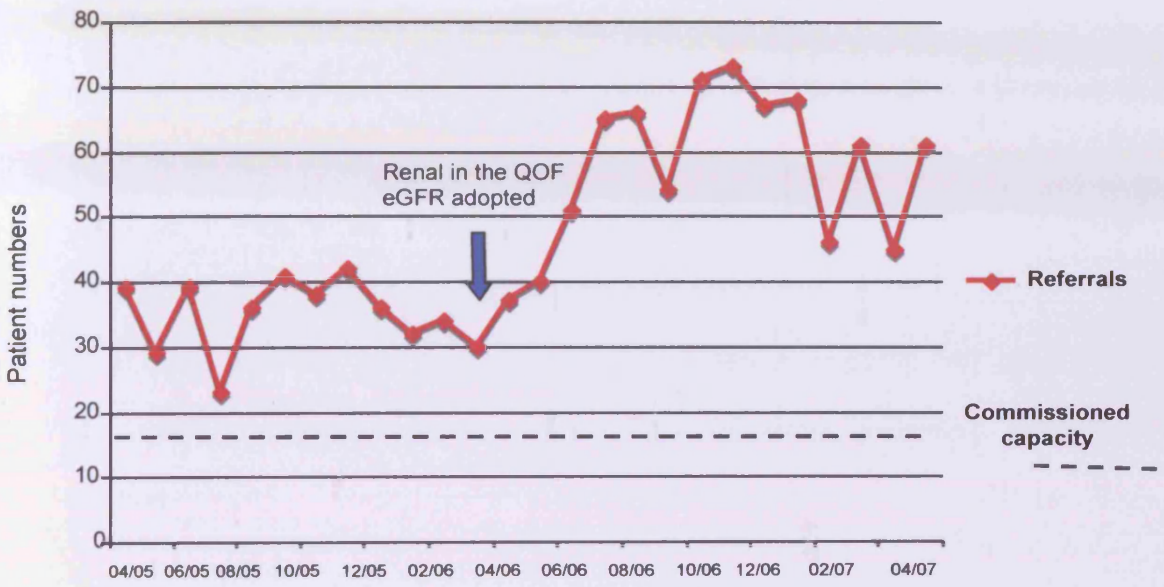
Having collected and collated renal outcome data on their patients, primary care practitioners have received extensive guidance on appropriate referral of patients for nephrology opinion from many sources including advice from the Royal College of General Practitioners [142].

6.4.3 Impact of eGFR and Renal QOF Introduction

The introduction of the eGFR and the renal Quality Outcomes Framework in Wales has had an impact both on nephrology referral and pathology requests. The scheme has been piloted and reported in the Gwent area. The number of new patient referrals to Gwent has almost doubled since the introduction of the eGFR and renal QOF outcomes and is detailed in Figure 76 below. These data replicate data published recently by Richards et al [143] reporting the impact of the introduction of eGFR and a Disease Management Programme (DMP) in the West Lincolnshire Primary Care Trust where monthly referral numbers increased by 2.7 times the previous monthly average but then fell by 42% following introduction of the referral assessment service as part of the DMP in October 2005.

The impact of this number of referrals on the capacity of secondary care nephrology services in Wales, in the long term is not sustainable. However it should be noted that in the study by Richards et al after approximately six months, the authors identified that 'steady state' had been achieved, with an average of 5 new Stage 4 and 5 patients being identified, which was within the capacity of the local services. Unfortunately, the decrease in referrals has not been replicated in Wales where numbers continue to grow and are now running between 80 and 90 per month.

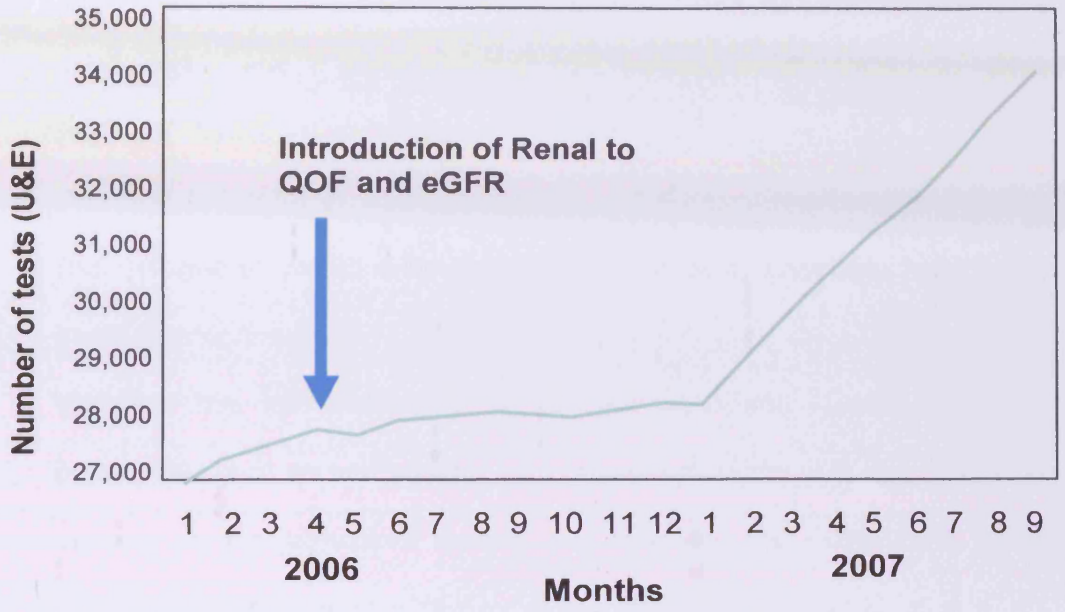
Figure 76: New Patient Referrals to Gwent



The impact of the introduction of eGFR reporting on the pathology services is detailed below in Figure 77. Monthly levels of Urea and Electrolyte requests sent to Pathology rose from around 28,000 per month to 34,000 per month sixteen (16) months later. It should be noted that the increase in uptake was not really apparent until April 2007 although eGFR and the QOF had been in place since April 2006. This could be accounted for by the fact that despite the outcome measure for undertaking eGFR being required in April 2006, payments were not made available until April 2007.

It is clear that the identification of renal disease impacts not only upon nephrology services but also upon those services providing pathology support.

Figure 77: Impact of QOF and eGFR on Gwent pathology services



6.4.4 Impact on Quality and Outcomes of Referrals

Since the completion of the work associated with this thesis, an audit of the quality and outcomes of this increase in referrals has been carried out. This audit would determine if each referral had sufficient information to allow nephrologists to decide

a) Whether the referral was appropriate – did this patient need to see a nephrologist or would referral to another medical speciality have been more appropriate?
b) Whether the information provided was sufficient – with particular emphasis on if renal function was abnormal what was the historical context of this abnormal finding and whether the information given enabled appropriate prioritisation of the referral in relation to others?

The audit was extended to look at the outcome of the first outpatient appointment to see whether each referral could have been dealt with differently.

Audit Results

Of the new referrals, seventy six percent (76%) came from Primary Care, with twenty four percent (24%) from Secondary Care and are illustrated in Figure 78 below.

Of these referrals, analysis was then undertaken of the appropriateness and quality of the referrals to understand whether the guidelines provided sufficient information to enable non-nephrologists to refer appropriately (Figure 79). Fifty seven percent of the patient referrals were given outpatient

appointments, 13% of the referrals were inappropriate and 30% had inadequate information to enable a decision to be made. In addition, analysis was then undertaken of the outcome of the first outpatient referral to assess whether these referrals had been appropriate (Figure 80). Of the patients given outpatient appointments, 71% had at least one follow up appointment, 19% were discharged from follow-up after one appointment, 9% did not attend for appointment and 1% were referred to the renal replacement therapy service.

Figure 78: Origin of new referrals to Gwent Nephrology Service (Percentage)

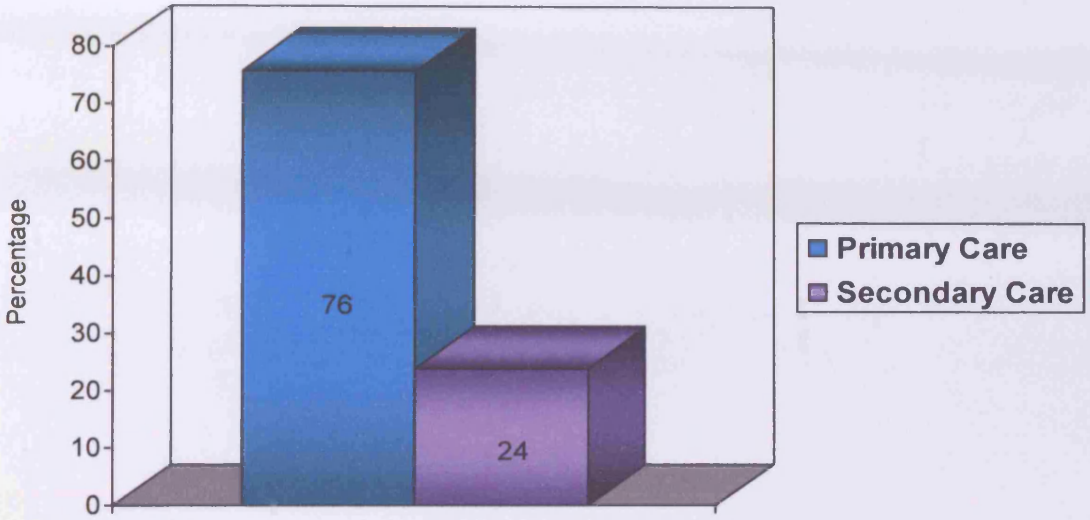


Figure 79: Quality of "New" Referrals to Gwent Nephrology Service

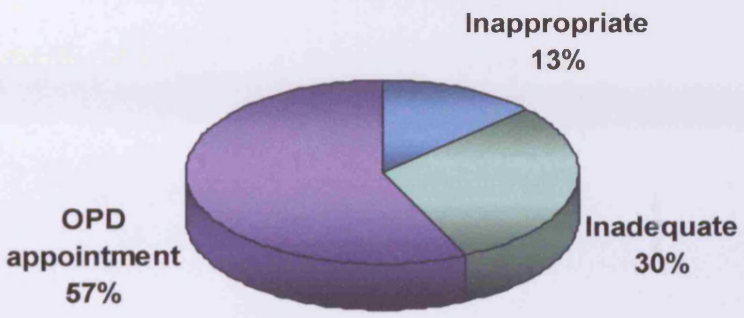
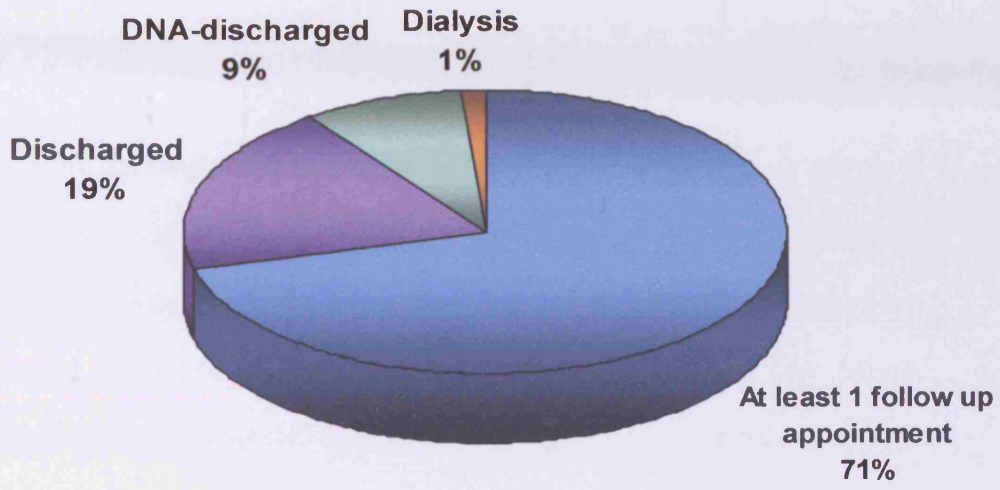


Figure 80: New Referrals - Out-patient outcome



6.4.5 Care Pathway Development

- A care pathway will be developed for the care of people at risk of renal disease and how the progression of the disease will be delayed through proactive management.

The work highlighted in this thesis, recognises that it is not possible for Nephrology services to do everything required to screen and manage care of patients with renal disease. It also recognises that the partnership of primary and secondary care and that the management of that interface is the key to success. In combination with the work of the NSF the emphasis is focused on a more structured referral pathway based on Renal Association and Royal College of General Practitioner guidelines [142]. The development and introduction of a care pathway in Wales has needed the cooperation and involvement of Local Health Boards, Local Medical Committees and support from the Welsh Assembly Government. The challenge of managing the increase in patient numbers within limited resources and ensuring appropriate timely referrals is essential.

The first objective in Wales is to run a pilot of a care pathway in Gwent and following a period of assessment and redesign, as necessary to extend the pathway to the rest of Wales. The pathway is designed to manage patient entry and exit from Nephrology services. The care pathway will utilise the Map of Medicine, Nephrology Pathway on http://www.mapofmedicine.com/ to create a shift to:

- Better use of local resources

- Increase collaboration among GPs and secondary care to improve patient care
- Mobilise the local health organisation and align it with the new pathways.

The Map of Medicine is accessible to all Health Care Professionals and consists of flow charts with information 'i' boxes to help in the decision making process. The information in the 'i' boxes can be updated on a regular basis as the evidence base changes. It should be noted that this development is dependent upon the skills and interests of individuals in using Information technology to support their practice. In common with other IT initiatives, care will have to be take to ensure that all members of the multi-disciplinary team have appropriate skills and have access to appropriate equipment during their working day. If this is not so, then the use of these tools may be restricted. An essential addition to the pathway is the incorporation of a referral proforma (Figure 81), acceptance of which was key to the successful implementation of the pathway.

Figure 81: Referral Proforma

Chronic kidney disease Referral Proforma – Gwent Health Community

Patient details Name dob Address NHS number Hospital number Postcode M / F Home tel no Mobile tel no Ethnic origin	**GP Details** Name Address or practice stamp Fax number Date of referral
History and examination: • General medical history • Medication including recent changes • Examination (especially BP, oedema)	
Previous results: All previous serial eGFR (creatinine) results with dates Results of renal USS if available (although this should not necessarily delay referral)	**Current results:** Urine dipstick results for blood and protein urine PCR (if indicated) Blood count eGFR serum creatinine urea potassium albumin calcium phosphate cholesterol PTH (if indicated)

Please send/fax to: Nephrology Unit, Royal Gwent Hospital, Newport on 01633-234798

To discuss patient's condition, please telephone: 02920 748467

6.5 Models of Care and Workforce Issues

The importance of collaboration between Primary and Secondary Care has been emphasised in chronic disease conditions other than CKD in particular the use of 'stepped care' models [144] [145]. In these models, hospital consultant staff work closely with GPs and may undertake clinics in Primary Care. Patient care is organised in four levels ranging from care delivered entirely in Primary Care to that delivered entirely in Secondary Care. Within the stepped care model, GPs are responsible for the initial diagnosis and initiation of treatment, with nurses playing a prominent role in following up and managing patient progress. Specialist care is provided as necessary with the most complex cases being taken over entirely by Secondary Care.

The role of Information Technology has been highlighted as an essential component of chronic disease management at the interface between Primary and Secondary Care [146] . Klebe and his colleagues highlight the input of the Department of Health in producing an information strategy for renal services which recommends that electronic care plans should be developed which can be shared across the care interface. The strategy includes the integration of clinical records and a facility for calculating GFR and utilising existing patient data to identify patients with CKD. In addition, the authors are currently setting up a clinical decision making support system for nephrology.

Patient self management is considered to be an essential component of a successful chronic disease management programme. Information technology has been used to set up Renal Patient View https://www.renalpatientview.org/ which enables computer literate individuals to view and share their own results and information. This information will enhance the experience of a

group of patients with CKD and empower them with information to help them manage their own treatment provided that sufficient safeguards on data protection and confidentiality can be guaranteed.

6.6 Implementation

The focus of much of the implementation and operationalisation of the care of patients at 'high risk' of developing renal failure has been around the education and development of the knowledge base of the medical staff, both in Primary and Secondary Care.

However, evidence from Primary Care itself suggests that responsibility for much of this work will ultimately be the responsibility of the nursing staff. Work from Brighton and Hove Primary Care Trust http://www.brightonandhovepct.nhs.uk/healthprofessionals/generalpractice/qualityindicators/documents/NURSEROLEinGMSQOF200607update.doc has highlighted that at least two of the QOF renal targets and outcomes are measured and operationalised by members of the Primary Care nursing team. The role, education and training of nurses involved in the care of this patient group will be paramount.

A combination of the adoption of the care pathway and the work done in this thesis encompasses both nurse led management and nurse led referral of patients and is generalisable to all geographical areas of Wales.

6.6.1 Secondary Care

The entire focus of care within Nephrology in Secondary Care is around preparation for dialysis including patient education and renal replacement therapy and its management. In undergraduate nurse training, input on renal issues remains focused on renal failure issues in particular and although the focus is changing onto chronic disease management, it is still around the management of those with the disease rather than focusing on preventing or slowing disease development.

All follow- up care of the numerically large group of patients who would benefit from preventive care is focused around medical follow up in secondary care with very little nursing input. It is possible that lessons could be learned from the development of the anaemia coordinator role within secondary care, as the similarities in the role requirement are evident - The patient group is large; the evidence base is good; patients require regular and ongoing monitoring and changes in therapy, the interface between primary and secondary care is crucial to success.

The role of the Consultant Nurse has two key components which would make the development of this role, in preventative disease management, ideal. Part of the role of the Consultant Nurse is the remit to incorporate research into patient care. Having research skills would enable the evidence base on preventing disease to be kept up to date on an ongoing basis. This is a very important but often overlooked essential of having a viable, long term tool for disease management.

The second component is the management of nurse-led clinics. Large numbers of patients could be managed in the early stages of CKD by nurses in Primary and Secondary Care. As has been shown in Chapter 4, the input of a nurse specialist in conjunction with expert advice from consultant nephrology staff, as required, had an impact on alterations made to patient therapy at the Primary and Secondary Care interface, However, there is neither funding nor manpower available to make this a viable option for the future. It is possible that a Consultant Nurse could have an impact on large numbers of patients if the remit included the preparation, coordinating and updating of education, training and competency materials for use in Primary Care. This would enable patients to be dealt with appropriately in Primary Care and those who require specialist input to receive increasing input from Secondary Care as required.

6.6.2 Primary Care

The pressure on nurses in Primary Care to become involved in and take responsibility for the care of particular patient groups is heavy and it is important that the profile of renal disease is as high as other chronic disease states. It is incumbent on people who are promoting renal disease management to ensure that they engage with those individuals and ensure that the support they receive meets the professional development needs of the staff as well as the needs of the patient group. The education of Primary Care Professionals in evidence-based, appropriate and timely referral to Nephrology services will be an ongoing process which will require frequent and timely updating, as the evidence base changes and remains dependent, to a large extent, on the good will and enthusiasm of motivated individuals, rather than being part of permanently funded infrastructure support.

Anecdotal reporting from nurses working in Primary Care who attended education sessions run by the multi-disciplinary renal team highlighted the paucity of available information on the practicalities of screening patients. Whilst welcoming the pathophysiological knowledge and presentation of the evidence relating to blood pressure control, inclusion of training and information materials with basic information, for example for microalbuminuria screening – methods, appropriate equipment and timing of samples was felt to be one of the aspects which could be developed.

The issue of lack of training for Primary Care nurses is highlighted in a report from December 2007 published online at Health Care Republic. http://www.healthcarerepublic.com which stated that one in six nurses involved with QOF work had been asked to carry out tasks they felt were

beyond their competence. In addition, 30 per cent have been asked to carry out QOF-related work for which they had no formal training. A significant minority — 10 per cent — of nurses employed in practices said they would carry out QOF work allocated by their employer even if they had not been properly trained. The issue of adequate training, competence and supervision must be tackled to ensure long term success of any initiative.

Much education and training work is being undertaken by individuals in isolation and it would be useful to consider the model of 'Do Once and Share' highlighted by Klebe et al [146] where new Information Technology knowledge is shared across specialities nationally, thereby saving time and reducing duplication.

Nationally accredited education, training and competency packages based on work could be put into place to support nursing staff in both Primary and Secondary Care. This would have the best chance of success if it was facilitated by the involvement of national organisations involving Practice Nurse organisations and the Royal College of Nursing.

6.7 Conclusion

Increasing numbers of patients are living with chronic disease within a health care system that is set up, in the main, to cope with acute illness. Although it is clear that redesign of the service is necessary, as so often, the issue of use of funding lies at the heart of much of the discussion. Preventative medicine and the distribution of finite resources remains the most difficult question facing both clinicians and politicians. The philosopher, Isaac Singer Berlin, illustrated the predicament that preventative health care faces, by constructing the analogy of a bystander on a river bank watching increasing numbers of drowning men floating down the river. Having saved a few by heroic effort, the bystander is faced with a dilemma – should he continue to try in vain to continue rescuing the drowning or should he abandon those already in the water and run upstream to try and stop people falling or being pushed into the water?

It is simple, in the abstract, to set out long term goals for the prevention of disease but it remains much more problematic to divert funding into prevention if this has an impact on the care given to individuals already suffering from disease. Policy making tends to focus on the current situation rather than potential situations in the future and the spectre of newspaper headlines highlighting particular individuals who are either having no treatment or poor quality treatment for established disease can make it difficult for the longer term goals focusing on prevention and the slowing of progression of renal disease, to gain support.

Rigorous appraisal and re-evaluation of the use of current funding as well as injections of new funding are essential to redesign services for the future in primary, secondary and tertiary care.

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