Optimising blood pressure control in Māori and Pacific patients with type 2 diabetes mellitus and established diabetic nephropathy in New Zealand

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He Karakia Tīmatanga

He Hōnore

He korōria ki te Atua

He maungārongo ki te whenua

He whakaaro pai ki ngā tāngata katoa

Āmine

Dedication

This thesis is dedicated to the DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study patients and their families.

E mihi ana au ki ngā whanau nō Rarotonga, Kia orana

Ki ngā whanau nō Samoa, Si o ta alofa atu

Ki ngā whanau nō Tonga, Malo e lelei

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Ki ngā tāngata whenua, Tēna koutou, tēna koutou, tēna koutou katoa

Abstract

Diabetes mellitus is having a considerable impact on the health and well-being of Māori and Pacific people in New Zealand (NZ). The prevalence of diabetic nephropathy is high in these groups, who also have a heightened risk of progression to end-stage renal disease (ESRD).

Good blood pressure (BP) control is paramount to the prevention and delay of diabetic nephropathy. Success rates in achieving BP control through the utilisation of conventional healthcare approaches have been sub-optimal in comparison to the outcomes achieved in randomised controlled studies, therefore innovative and effective models of care for BP control are critically needed.

The aim of this thesis is to examine whether a novel, integrated, community-based model of care using nurse-led Māori and Pacific healthcare assistants (HCA) to manage hypertension in Māori and Pacific patients with type 2 diabetes and chronic kidney disease (CKD) is more effective than conventional care in reducing BP and delaying progression of cardiac and renal end-organ damage. The DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study was a randomised controlled trial of 12 months duration that examined this model of care. Our findings showed that this model of healthcare delivery is significantly more effective than conventional care in lowering systolic BP, and reducing cardiac and renal end-organ damage in these high-risk patients.

The thesis includes reviews and summaries which describe the respectively high prevalence of diabetes and diabetic nephropathy in Māori and Pacific people in NZ, and a cross-sectional analysis illustrates the high rates of Māori and Pacific people receiving renal replacement therapy (RRT), and the associated high co-morbidity and mortality rates, particularly in Māori patients with ESRD. The low rate of renal transplantation in Māori and Pacific people is also highlighted.

Barriers to healthcare and their impact on Māori and Pacific communities are summarised.

A literature review explores the effectiveness of different antihypertensive agents to achieve good BP control and delay renal progression in diabetic nephropathy. Another review looks at different approaches to BP control in the community.

The effectiveness of nurse-led hypertension clinics on BP control, cardiovascular (CV) and renal outcomes is also discussed in the thesis, and the key factors which contribute to making the nurse-led model of care effective are highlighted.

The training of the DEFEND study HCAs is described and their role in the DEFEND study is discussed.

A review on the benefits of 24-hour ambulatory blood pressure monitoring (ABPM) as a tool for diagnosis, treatment and CV outcome prediction precedes a discussion of the 24-hour ambulatory BP component of the DEFEND study, which was abandoned due to inadequate baseline results.

The thesis concludes with a discussion on the applicability of the DEFEND study model to routine outpatient care and outlines additional measures that could be taken to further enhance the effectiveness of this innovative model of healthcare delivery. This research has added to the current knowledge of models of healthcare delivery for BP control in the community. It demonstrates the effectiveness and likely ease of applicability of a novel model of care for controlling BP in Māori and Pacific patients with type 2 diabetes and established diabetic nephropathy, who are experiencing unacceptably poor health outcomes.

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He ora to whakapiri

There is strength in unity[1]

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Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
ACR	Albumin:Creatinine Ratio
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CC	Community Care
CKD	Chronic Kidney Disease
CV	Cardiovascular
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
GBM	Glomerular Basement Membrane
HCA	Healthcare Assistant
LA	Left Atrial
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
RAAS	Renin-Angiotensin-Aldosterone System
RCT	Randomised Controlled Trial
RRT	Renal Replacement Therapy
UAE	Urinary Albumin Excretion
UC	Usual Care

Introduction

E kore e hohoro e opeope o te otaota

A large force is not easily overcome[3]

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in New Zealand (NZ). Māori and Pacific people are over-represented in the ESRD population, with greater incidence rates compared to NZ Europeans, and this is predominantly due to diabetic nephropathy.[4] Chronic kidney disease (CKD) occurs earlier in Māori and Pacific people compared to NZ Europeans, and the rate of progression in renal function decline is more rapid.

This thesis commences by highlighting the differences in the prevalence of obesity, diabetes and diabetic nephropathy in Māori and Pacific people compared to NZ Europeans and the total NZ population. The higher rates of diabetes morbidity and mortality in Māori and Pacific people are also discussed.

The thesis discusses the contributory role of hypertension to the development of diabetic nephropathy and its progression to ESRD, and also reviews current knowledge on interventions to reduce its progression, including by the utilisation of antihypertensive agents and through the implementation of different models of healthcare delivery to achieve good blood pressure (BP) control.

Important barriers to healthcare exist for Māori and Pacific people, and the thesis discusses how these barriers contribute to the health disparities seen between these groups.

The primary focus of this thesis is to examine one innovative way of delivering healthcare to Māori and Pacific patients with established diabetic nephropathy that achieves good BP control, improves renal and cardiovascular (CV) outcomes, and is appropriate and acceptable to Māori and Pacific communities.

Chapter 1

1.1 Epidemiology of type 2 diabetes in New Zealand

Introduction

Over the last century, the era of global industrialisation has seen a marked transition in the disease profile of many population groups, shifting from a predominance of infectious diseases and nutritional deficiencies to chronic degenerative diseases, such as cardiovascular disease (CVD), cancer and diabetes.[5,6] Environmental and lifestyle changes have led to an increase in the prevalence of obesity, resulting from a decrease in daily energy expenditure due to less physical activity (work and non-work related) coupled with the widespread availability, greater affordability and resultant excessive consumption of energy-dense foods.[7] The increase in obesity prevalence has occurred in parallel with an increasing prevalence of diabetes.[7] The following chapter summarises the epidemiology of diabetes in New Zealand (NZ), comparing prevalence rates in Māori, Pacific people, and NZ Europeans to the total population.

Demographic shifts in New Zealand

The demographic profile of NZ has undergone much change over the last fifty years. Population size has increased from 2,403,600 in 1960 to 4,393,500 in 2010.[8] Māori have experienced a large demographic shift after years of urban migration from rural areas into towns and cities.[9,10] The urban Māori population increased from 26% in 1945 to more than 80% by the end of the 20th century.[9] Approximately fifty years ago, NZ's ethnic make-up began to diversify. The migration of people from several Pacific Island nations commencing in the 1960s,[11] followed by a more recent and continuing influx of migrants from Asia, have contributed to this diversity.[12] The NZ 2006 Census reported the indigenous Māori population to comprise 14.6% of the population, Pacific people 6.9%, Asian people 9.2% and NZ Europeans 67.6%.[13] The Pacific

population of NZ is mainly comprised of people of Samoan, Tongan, Cook Island, Niuean, Fijian and Tokelauan origin.[14] The demographic profile is also changing due to an increase in the ageing population.[15]

Obesity in New Zealand

The increasing prevalence of obesity in the community is having a considerable impact on the health of New Zealanders, in particular on Māori and Pacific people. Obesity is defined by the World Health Organisation as a body mass index (BMI) ≥30kg/m^2, and overweight is defined as a BMI between 25-29.9kg/m^2.[16] Obesity rates in NZ have increased substantially over the past three decades. From 1977 to 2003, the prevalence of obesity in NZ adults more than doubled, increasing from 9.4% to 19.9% in males, and from 10.8% to 22.1% in females.[17] The 2006/2007 NZ Health Survey (NZHS) showed that one in three adults was overweight (36.3%) and one in four was obese (26.5%).[18] Notably high obesity rates were evident in Māori and Pacific people, with 41.7% of Māori adults and 63.7% of Pacific adults reported as obese. These results are reinforced by cross-sectional data on Pacific people aged 20 years and older from church communities throughout Auckland showing an obesity prevalence of 45% in men and 66% in women.[19]

The disparities in obesity prevalence in NZ are also apparent in childhood. The 2002 National Children's Nutrition Survey reported a prevalence of being overweight or obese at 21.3% and 9.8% respectively in the total population, but showed a greater prevalence of overweight/obesity in Māori children (boys 19.6%/15.7%, girls 30.6%/16.7%) and Pacific children (boys 33.9%/26.1%, girls 32.9%/31.0%).[20] Another study looking at obesity rates in Auckland school children aged 5-10 years had similar findings, noting that Māori and Pacific children were more likely to be obese in comparison to NZ European children (Māori 16%, Pacific 24% vs NZ Europeans 8.5%).[21]

Type 2 diabetes in New Zealand

Attempts have been made to paint an accurate picture of the prevalence of diabetes in NZ[22,23] but a lack of up-to-date nationwide prevalence data has made this difficult, hence most of the data has been sourced from several population-based studies. These studies, undertaken in the early 1980s to 2008 include the respective Ministry of Health NZHS of 1996/1997,[24] 2002/2003[25] and 2006/2007[18] in addition to a number of household, workforce, community, primary and secondary care surveys.[19,26-36] While these studies report a variable range of diabetes prevalence for Māori and Pacific groups as well as for the total population, they all demonstrate a common and important feature: that diabetes prevalence rates are higher in Māori and Pacific people compared to NZ Europeans or the total population. The 2006/2007 NZHS reported a prevalence of doctor-diagnosed diabetes of 5.0% (4.6-5.5) in the total population, equating to 157,100 people with diabetes, the majority having type 2 diabetes [90.9% (88.3-93.7)].[18] The respective diabetes prevalence rates by ethnicity were NZ Europeans 4.3%, Māori 5.8%, Pacific people 10.0%, and Asians 6.5%. Age-adjusted rates showed that the prevalence was greater in Māori, Asian and Pacific people in comparison to NZ Europeans, with Pacific people having a 3-fold greater likelihood of diabetes than the total population. The other population-based studies have reported diabetes prevalence rates ranging from 5.2% to 34.1% in Māori and from 4.0% to 25.0% in Pacific people.

The South Auckland Diabetes Project conducted a large cross-sectional survey from randomly selected households between the years 1991-1994, screening subjects aged 40-79 years for diabetes, using a random blood glucose and inviting those with an elevated result, in addition to 20% randomly selected subjects with a normal screening result, to undergo a 75 gram oral glucose tolerance test (OGTT).[26] While the diabetes prevalence in NZ Europeans aged 40-59 years was 7.5% (6.2-9.0), it was higher among Māori at 21.1% (16.6-25.6) and Pacific people at 25.0% (19.8-30.1), with higher obesity rates seen in the Māori and Pacific subjects overall (Māori 63%, Pacific 69%, NZ Europeans 26%).

A high prevalence of diagnosed diabetes in Māori and Pacific people was also demonstrated in a cross-sectional survey on all patients registered with 10 primary care practices in the Lakes District Health Board (DHB) area.[33] 1,819 patients had diagnosed diabetes. The age–standardised diabetes prevalence was highest in Māori and Pacific people compared to NZ Europeans, showing a 3-fold greater likelihood of having diabetes in the 40 years and older age groups. An expected discrepancy in prevalence rates was seen between the most deprived and the least deprived NZ European patients, with a higher prevalence of diabetes seen in the most deprived group. A somewhat surprising finding was a similarity of diabetes prevalence in the most deprived Māori patients when compared to the least deprived Māori patients, with the highest overall rates of diabetes prevalence seen in the least deprived Māori patients (9.7% males, 6.2% females). This is contrary to the usual trend which was seen in the NZ European group, where diabetes prevalence has an inverse relationship to socio-economic status.[37]

High prevalence rates were noted in an Auckland Surgical Ward Study (1990-1991), with diabetes present in 18.3% to 31.7% of Māori and 16.1% to 30.2% of Pacific patients (aged 40-69 years).[34] In comparison, NZ European rates were only 6.0% to 7.9%. The incidence of diabetes increases with age, and the Ngati Porou Hauora Register Study, a Māori-specific study of 589 subjects demonstrated high rates of diabetes in older Māori, reporting an overall age-standardised prevalence of diabetes of 10.6%, reaching a notably high prevalence rate of 34.1% in the 60-69 year age group.[35] This is in comparison to 2006/2007 NZHS data which showed a diabetes prevalence of 15.5% in men and 12.3% in women aged 65-74 years.[18]

An increasing prevalence of type 2 diabetes in young people has been observed throughout different parts of the world in the last two decades, coupled with the rising incidence of obesity in youth.[38,39] An increasing prevalence of type 2 diabetes has also been reported in NZ youth. A 1996 survey of adolescents attending an Auckland Hospital adolescent diabetes clinic was compared to a

follow-up survey conducted in 2002.[40] The numbers of patients with type 2 diabetes increased by 9-fold over the six year interval, with Māori and Pacific adolescents being the predominant ethnic groups affected. These findings were reinforced by other studies including a retrospective review of epidemiologic and clinical data of Northland Māori patients diagnosed with diabetes prior to the age of 30 years.[41] The study showed an occurrence of type 2 diabetes at an earlier age than expected with an average age at diagnosis of type 2 diabetes of 19.1 years. Obesity and hypertension were more common in the subjects with type 2 diabetes compared to the group with type 1 diabetes. Another retrospective study conducted in the Waikato region which reported on 251 patients under 26 years of age with diabetes demonstrated that of the 13 patients diagnosed with type 2 diabetes, the majority (7 out of 13) were Māori.[42]

Overall, Māori and Pacific patients with type 2 diabetes are younger than NZ European patients. One large study reviewed records of 13,281 patients with diabetes, attending 242 general practices in NZ, who were enrolled between August 2000 and May 2003 in the *Get Checked* programme, a nationwide Ministry of Health-initiated programme, launched in 2000, providing patients with diabetes a free annual check from their medical practitioner, subsequently replaced by a community and primary care based programme, termed the *Diabetes Care Improvement Package* in 2012.[43,44] The study found that Māori and Pacific patients with type 2 diabetes were younger than NZ European patients (mean age for Māori/Pacific 56.8 years vs NZ European 66.7 years $p<0.001$).[44] NZ Ministry of Health data has also shown that the average age at diagnosis of diabetes is several years younger in Māori and Pacific people (47-48 years) compared to NZ Europeans (54 years).[45]

The impact of type 2 diabetes on Māori and Pacific people

The health status of Māori and Pacific patients with diabetes differs considerably from that of NZ European patients. In the *Get Checked*

programme, the health status between the different ethnic groups within the study was compared, and found that Māori and Pacific patients had higher BMIs, higher diastolic BP and poorer glycaemic control, were more likely to smoke and were less likely to have undergone retinal screening. Overall, the risk for microvascular complications in Māori and Pacific patients was higher.[44]

Diabetes-related complication rates for both micro- and macrovascular disease are higher in Māori and Pacific people than NZ Europeans despite their younger age at diagnosis of diabetes.[22,23,27] The difference in prevalence rates of diabetic retinopathy was well illustrated in the South Auckland Diabetes Project household survey.[46] The study showed that while there was no difference between Māori, Pacific and NZ Europeans in the prevalence of diabetic retinopathy overall, the prevalence of moderate to severe diabetic retinopathy was higher in Māori (12.9%) and Pacific patients (15.8%) compared to NZ European patients (4.0%). Diabetic nephropathy is discussed in Chapter 1.3. Major foot complications secondary to peripheral neuropathy or peripheral vascular disease (amputation, ulceration) have been found to have a higher prevalence in Pacific patients compared to Māori and NZ European patients.[47] There is limited epidemiological data on CV and cerebrovascular disease in patients with diabetes in NZ.

Ethnic differences are apparent in mortality rates from diabetes in NZ, with Māori and Pacific people having a several-fold greater likelihood of dying from diagnosed diabetes than NZ Europeans.[45] High mortality rates were seen in Māori patients in a cohort of 9043 patients with diabetes, which found that while NZ Europeans had similar standardised mortality rates to the general population [males 1.16 (1.05-1.28), females 1.10 (0.98-1.24)], mortality rates in Māori males and Māori females were 2.49 (2.06-3.01) and 3.12 (2.56-3.80) respectively.[48] Also, Māori patients in the cohort were more likely than European New Zealanders to die from CVD and cancer, and had a higher risk of death from nephropathy (Hazard–ratios: CVD 2.31 (1.6-3.3), cancer 1.83 (1.1-3), and nephropathy 11.74 (4.8-29)).[48] Another study demonstrated this difference

in nephropathy-related mortality rates between Māori and NZ Europeans with diabetes, where risk of death was 13.1-fold greater in Māori.[49] Similarly, a further study linked national hospital discharge records with mortality records to compare the mortality patterns of Māori, Pacific and non-Māori/non-Pacific patients with diabetes to the general population of the same ethnic group.[50] 74,847 patients (11,268 Māori, 5,730 Pacific, and 57,849 non-Māori/non-Pacific) aged over 25 years who were discharged from a NZ public hospital between 1988 and 2001, with a diagnosis of diabetes coded on the hospital discharge summary were included in the study. 29,295 (39%) patients in the cohort had died by the end of 2001. Age-adjusted standardised mortality ratios (SMR) based on the underlying cause of death were calculated for each ethnic group. All cause SMRs were higher in Māori men (3.44 [95% CI: 3.30-3.58]), and women (3.80 [95% CI: 3.64-3.97]), compared to Pacific people (men 2.41 [95% CI: 2.21-2.61] women 2.23 [95% CI: 2.06-2.41]) and non-Māori/non-Pacific groups (men 2.98 [95% CI: 2.93-3.04] women 2.99 [95% CI: 2.93-3.04]), showing a pattern of excess mortality amongst Māori with diabetes.

Conclusion

The high prevalence rates of diabetes in Māori and Pacific people in NZ partly explains the high incidence of diabetic nephropathy in these groups. Māori and Pacific people are diagnosed with type 2 diabetes at an earlier age, and are therefore more likely to develop diabetes-related micro- and macrovascular complications, given the longer duration of diabetes. However, the high incidence of diabetic nephropathy and ESRD cannot be fully explained by the longer duration of diabetes in Māori and Pacific people, as the incidence rates of renal disease in these groups are over and above their respective prevalence rates of diabetes. Chapter 1.3 highlights the differences between Māori and Pacific people and NZ Europeans in the rate of progression of diabetic renal disease.

1.2 Diabetic nephropathy

Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in New Zealand (NZ), Australia and the United States, accounting for 50.9% of new patients commencing renal replacement therapy (RRT) in NZ in 2010.[4] It has a strong association with cardiovascular (CV) morbidity and mortality.[51] Diabetic nephropathy is a clinical syndrome characterised by a constellation of structural and functional abnormalities of the kidneys that can occur in patients with diabetes. Glomerular hypertrophy and hyperfiltration occur, which can lead to a sustained increase in the rate of urinary albumin excretion (UAE). Increased UAE is a strong predictor for a decline in renal function and correlates with the severity of renal damage. The early clinical stage of diabetic nephropathy, microalbuminuria, is defined as a UAE rate of 30-300mg/24-hours.[52] Macroalbuminuria or proteinuria, defined as a UAE rate of >300mg/24-hours, signifies more advanced renal disease.[52] A decline in glomerular filtration rate (GFR) can occur from the onset of microalbuminuria[53] and can progress to the point of ESRD requiring RRT.

Natural history

Microalbuminuria is one of the earliest clinical signs of diabetic nephropathy,[52] and signals that a disruption of the previously impermeable glomerular filtration barrier has occurred, allowing negatively charged proteins the size of albumin to pass through it.[54] The European Diabetes (EURODIAB) Prospective Complications group found a cumulative incidence of microalbuminuria of 12.6% in patients with type 1 diabetes (95% confidence interval 10.7-14.7%) over a 7.3 year follow-up period.[55] Similar results were seen in the Microalbuminuria Collaborative Study Group, which found a cumulative incidence of 14.5% over 7 years.[56] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a 25% prevalence of microalbuminuria in patients with type 2 diabetes 10 years after diagnosis of diabetes.[57] There is evidence

that patients with a UAE rate in the higher range of normal have an increased risk of developing microalbuminuria.[58]

Approximately 30-45% of patients with type 1 diabetes and microalbuminuria will develop macroalbuminuria over 10 years.[59] Approximately 20-40% of patients with type 2 diabetes and microalbuminuria will develop macroalbuminuria.[60] The progression to macroalbuminuria has declined over the past two decades, with early studies of diabetic nephropathy in type 1 diabetes showing progression of microalbuminuria to macroalbuminuria in approximately 80% of patients.[61,62] The observed decrease may be secondary to improvements in the approach to glycaemic and BP control, and the introduction of renin-angiotensin-aldosterone system (RAAS) blocking agents.[59]

A gradual decline in GFR occurs during the microalbuminuric phase, but once macroalbuminuria has developed, there is a progressive decline in GFR, which is highly variable between individual subjects (2-20ml/min/year).[52] This decline can continue until ESRD has occurred and RRT is required. Approximately 50% of patients with type 1 diabetes will develop ESRD within 10 years of the onset of macroalbuminuria and 75% will have reached ESRD by 20 years.[52] However, only 20% of patients with type 2 diabetes and macroalbuminuria will have developed ESRD by 20 years.[52] Patients with chronic kidney disease (CKD) are more likely to die from CVD before developing ESRD.[51]

Pathology

Diabetic nephropathy is typically characterised by glomerular basement membrane (GBM) thickening and mesangial expansion, which can lead to a reduction in the glomerular filtration surface size.[63] Mesangial expansion can occur either diffusely, termed diabetic glomerulosclerosis or in a nodular pattern (Kimmelstiel-Wilson nodules). The glomerular podocytes, renal tubules, interstitium and arterioles can also undergo structural change.[64] The typical glomerulopathic changes of diabetic nephropathy are more frequently seen in patients with type 1 diabetes. Patients with type 2 diabetes are more likely to

have complex and heterogeneous structural changes and are less likely to exhibit typical diabetic glomerulopathic changes.[65]

Screening and diagnosis

Screening for microalbuminuria should be performed at the time of diagnosis for all patients with type 2 diabetes, as undiagnosed diabetes may have been present for an undefined period prior to diagnosis and microalbuminuria may already be present.[57] Guidelines recommend screening for albuminuria at 5 years following the diagnosis of type 1 diabetes.[66] However, screening for microalbuminuria should be considered earlier than this in patients with poor glycaemic, BP or lipid control.[67] Microvascular disease can be accelerated over the pubertal period, so screening should occur within 2 years following the onset of puberty.[68] The impracticalities and potential for errors involved in collecting 24-hour or timed urinary specimens have led to these methods being superseded by the urinary albumin to creatinine ratio (ACR) which can easily be calculated on an untimed urine specimen.[52] Microalbuminuria is diagnosed if urinary ACR is persistently ≥2.5mg/mmol in males and ≥3.5mg/mmol in females. A urinary ACR ≥30mg/mmol is approximately equivalent to a UAE rate ≥300mg/24-hours, or macroalbuminuria. A diagnosis of microalbuminuria should be made after 3 positive tests have been recorded over a 3-6 month period.[52] Potential factors that can cause a transient elevation of the UAE rate include urinary tract infection, acute febrile illness, poor glycaemic control, poorly controlled hypertension, decompensated heart failure and vigorous exercise.[69] A diurnal variation exists in the UAE rate of individuals.[52] Given this, a spot urine specimen is best collected in the morning, and a first-void specimen is preferred.

It is recommended that an estimation of GFR be carried out as part of the routine screening for diabetic nephropathy.[66] The equation for GFR estimation recommended in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™) Clinical Practice Guidelines is the study of

Modification Diet in Renal Disease (MDRD) equation.[66] However, this equation underestimates GFRs over 60ml/min/1.73m^2, and is likely to be superseded by the CKD Epidemiology Collaboration (CKD-EPI) equation which has greater sensitivity to detect CKD in subjects with GFRs over 60ml/min/1.73m^2.[70] Once screening has commenced, guidelines recommend annual screening of GFR and urinary ACR if the patient has normal renal function and is normoalbuminuric.[66]

Risk factors for developing diabetic nephropathy

a) Hyperglycaemia

Hyperglycaemia is an important risk factor in the development of diabetic nephropathy.[56,71,72] It is associated with the production and accumulation of advanced glycation end-products, which subsequently lead to the production of specific cytokines and growth factors through stimulation of intracellular signaling molecules.[73] The synthesis of cytokine mediators such as transforming growth factor (TGF) β are driven by hyperglycaemia and/or intra-glomerular hypertension, and can lead to an overproduction of matrix protein.[74] Mesangial expansion occurs secondary to an imbalance between the production and degradation of mesangial matrix protein, resulting in accumulation of matrix protein.[63] Together with elevated systemic BP and intra-glomerular pressures, kidney damage occurs. Renal biopsy studies comparing histological differences between identical twins discordant for type 1 diabetes have shown greater GBM and mesangial dimensions in the twin with diabetes.[75] Both the Diabetes Control and Complications Trial (DCCT) and the UKPDS showed that the risk of developing microalbuminuria can be reduced by achieving intensive glycaemic control.[76,77] In the UKPDS, a reduction in HbA1c by 1% was associated with a 37% decrease in microvascular endpoints.[77]

b) Hypertension

Hypertension is also a major risk factor for both the development and progression of diabetic nephropathy.[72] The UKPDS showed that a 13% reduction in the risk of microvascular endpoints could be achieved with every 10mmHg

drop in systolic BP.[78] Patients with type 1 diabetes and normoalbuminuria have a similar prevalence rate of hypertension to that of the general population.[79] Hypertension in type 1 diabetes is often caused by underlying diabetic nephropathy,[52] becoming apparent after the onset of diabetic nephropathy. However, there is evidence that patients with type 1 diabetes who are at risk of developing microalbuminuria are more likely to experience a loss of nocturnal BP dipping, preceding the onset of microalbuminuria, when compared to normoalbuminuric patients.[80] In type 2 diabetes, a third of patients will have hypertension at the time of diagnosis of diabetes.[78] In these patients, hypertension may be secondary to underlying diabetic nephropathy or essential hypertension, and less commonly, due to secondary causes such as renovascular disease.

c) Hyperfiltration

Hyperfiltration is a common finding early in the course of diabetes, and appears to be a key mediator in the pathophysiological pathway leading to diabetic nephropathy, and has been shown to predict the development of microalbuminuria and progression of nephropathy.[62,81] An early study by Mogensen and Christensen looking at the natural history of diabetic nephropathy in patients with type 1 diabetes, found that patients who developed overt nephropathy exhibited elevated GFRs early in the course of their diabetes compared to those in whom macroalbuminuria did not develop.[62] This was reinforced by a meta-analysis of ten cohort studies which included 780 patients with type 1 diabetes, and showed that subjects with hyperfiltration early in the course of their diabetes were at an increased risk of progression to diabetic nephropathy.[82] A correlation has been demonstrated between glycaemia and GFR, where subjects exhibiting impaired glucose intolerance have an increased GFR compared to subjects with normal glucose tolerance, but have a lower GFR compared to subjects with newly diagnosed diabetes.[83]

d) Smoking

In patients with both type 1 and type 2 diabetes, smoking is a risk factor for microalbuminuria.[84,85] The likelihood of developing microalbuminuria becomes synergistic when smoking and hyperglycaemia are concurrent in patients with type 1 diabetes.[86]

e) Dyslipidaemia

Dyslipidaemia is another important risk factor for diabetic nephropathy.[72] Elevated plasma triglycerides and low HDL concentrations have been associated with the development of diabetic nephropathy.[72]

f) Genetics

Familial clustering of diabetic nephropathy has been noted in patients with both type 1 and type 2 diabetes, conferring a higher risk of diabetic nephropathy in first-degree relatives of subjects diagnosed with diabetic nephropathy.[87-89] A full description of the genetics of diabetic nephropathy is beyond the scope of this thesis.

Diabetic nephropathy and macrovascular disease (mortality)

Microalbuminuria is not only an important predictor of progression to macroalbuminuria and ESRD, but has also been shown to be a predictor of all-cause mortality in the general population.[90,91] Studies from the early 1980s showed microalbuminuria to be predictive of increased total and CV mortality in patients with both type 1 and type 2 diabetes, with mortality rates increasing with progressively higher levels of albuminuria.[61,92] A meta-analysis of 11 cohort studies concluded that microalbuminuria was a strong predictor of total and CV mortality and CV morbidity in patients with type 2 diabetes, with an overall odds ratio of 2.4 (95% confidence interval 1.8-3.1) for death and 2.0 (95% confidence interval 1.4-2.7) for CV mortality and morbidity.[93] In the Heart Outcomes Prevention Evaluation (HOPE) Study, patients with diabetes and microalbuminuria had a 1.97-fold (95% confidence interval 1.68-2.31) greater

risk for a composite outcome of myocardial infarction, stroke or CV death, and a 2.15-fold increased risk for all-cause mortality, compared to patients with diabetes and no microalbuminuria.[94] In addition to an increased risk of CVD, the risk of heart failure increases as UAE rate increases in people with type 2 diabetes.[95] A reduction in GFR has been shown to be associated with an increased prevalence of both CV risk factors and CV outcomes.[51] The risk of death, CV events and hospitalisation increased with a declining GFR within a large, diverse population of 1,120,295 adults.[96] The National Health and Nutrition Examination Survey (NHANES) II study found that the number of CV risk factors increased with each progressive stage of CKD.[97] The Hypertension Detection and Follow-up study showed that an elevated serum creatinine at baseline was a potent independent risk factor for mortality, with a 3-fold greater likelihood of death within 8 years in subjects with renal function decline compared to subjects with normal renal function.[98] CV mortality is 10 to 20-fold higher in dialysis patients compared to the general population.[99]

Diabetic nephropathy and macrovascular disease (morbidity)

A high prevalence of atherosclerotic disease has been reported in patients with CKD compared to the general population[100] and the incidence of atherosclerotic disease, left ventricular hypertrophy (LVH) and heart failure is substantial in haemodialysis patients.[101] Pressure overload secondary to hypertension can lead to LVH, while fluid overload can lead to volume overload, LV dilatation, and LVH. These haemodynamic abnormalities can result in diastolic and systolic dysfunction and cardiac failure.[102] The latter is a potent marker of poor outcomes in patients on dialysis.[102] In ESRD, calcification frequently occurs within atherosclerotic lesions, augmenting the severity of vascular disease.[103]

Diabetic nephropathy and the metabolic syndrome

One of the main reasons for increased CV morbidity and mortality is that patients with diabetes and microalbuminuria have a higher prevalence of traditional CV risk factors and features of the metabolic syndrome, compared to

patients with diabetes and no microalbuminuria.[51,95] An increased prevalence of dyslipidaemia, hypertension and other traditional risk factors is also seen in patients with a reduced GFR.[100] After adjustment is made for traditional CV risk factors, a progressive reduction in GFR is still associated with a heightened risk for CV outcomes, suggesting that CKD is an independent risk factor for CVD.[51] Non-traditional CV risk factors such as elevated inflammatory markers, oxidant stress and abnormal calcium and phosphorus metabolism may be important contributors to the heightened risk for CVD in CKD.[51] Albuminuria has been associated with insulin resistance, endothelial dysfunction, transmembrane leakiness, and a prothrombotic state, and appears to be a marker of generalised vascular dysfunction,[104] therefore potentially signalling the presence of endothelial dysfunction elsewhere, increasing the risk of atherosclerosis and CV events.

Summary

Many patients with both type 1 and type 2 diabetes develop microalbuminuria. A considerable proportion will go on to develop macroalbuminuira and ESRD. Diabetic nephropathy is a predictor of increased risk of CV events, especially with advancing renal disease.

1.3 Diabetic nephropathy in Māori and Pacific people in New Zealand

Cross-sectional evaluation of Māori and Pacific patients with diabetes and end-stage renal disease receiving renal replacement therapy.

Introduction

The incidence and prevalence rates at each stage of diabetic nephropathy are higher in Māori and Pacific patients[105] and these groups are over-represented in the end-stage renal disease (ESRD) population in New Zealand (NZ), where diabetes is the leading cause.[106,107] McDonald and Russ's paper on the burden of ESRD among indigenous peoples of Australia and NZ reported that patient age at commencement of dialysis is approximately 10 years younger in the indigenous group, compared to non-indigenous population.[108] The Australian and NZ Dialysis & Transplant Registry (ANZDATA), formed by Kidney Health Australia and the Australian & New Zealand Society of Nephrology records the prevalence, incidence and outcome of dialysis and transplant treatment for patients with ESRD in Australia and NZ. It consequently holds an extensive and invaluable epidemiological database of ESRD in Australia and NZ. The following cross-sectional evaluation is derived from the findings in the 34th ANZDATA Report 2011,[4] containing the 2010 data. The second part of this chapter summarises the differences in diabetic nephropathy and the rate of progression to ESRD in Māori and Pacific people compared to NZ Europeans. The third part of this chapter briefly discusses the costs of RRT in people with ESRD secondary to diabetes in NZ.

End-stage renal disease population in New Zealand

At the end of 2010, a total of 3,820 people were receiving RRT in NZ. 2,378 patients were receiving dialysis treatment while 1,442 patients had a functioning renal transplant. Table 1 shows the total number of patients by ethnicity receiving RRT, and all new patients receiving RRT in 2010. In comparison to the 2006 Census population percentages for different ethnic

groups,[13] the higher rates of Māori and Pacific patients receiving RRT becomes apparent.

Table 1: End-stage renal disease patients receiving renal replacement therapy in New Zealand in 2010

Ethnicity	Total no. on RRT *n* (%)		New RRT patients *n* (%)		2006 Census Population[13] Percentages %
Māori	889	(23.4)	154	(30.6)	14.6
Pacific	627	(16.5)	106	(21.1)	6.9
Caucasian	1,965	(51.8)	199	(39.6)	67.6
Asian*	294	(7.8)	36	(7.2)	9.2
Other	18	(0.5)	8	(1.6)	0.7
Total	**3,793**		**503**		**100.0**

***Asian patients included patients of Chinese, Malay, Indian and Vietnamese ethnicity**

RRT=renal replacement therapy

Primary cause of end-stage renal disease

The leading cause of ESRD in all new patients commencing RRT in 2010 was diabetic nephropathy, reported as the primary renal disease in 50.9% of new patients, with type 2 diabetes responsible for 95.3% of diabetic nephropathy cases. The second and third most common causes were glomerulonephritis and hypertension respectively. Diabetes was the predominant cause of ESRD in the majority of new Māori and Pacific patients in 2010 (73.4% and 68.9% respectively). Glomerulonephritis was the second most common cause of primary renal disease, seen in 15.6% of new Māori patients and in 17.9% of new Pacific patients. Hypertension was the primary cause in 5.2% of new Māori patients and 4.7% of new Pacific patients. The most common cause of new primary renal disease in Caucasian patients was glomerulonephritis, followed by diabetes and hypertension. Diabetes was the most common cause of primary renal disease in Asian patients, followed by glomerulonephritis and hypertension. See table 2 below.

Table 2: Primary cause of end-stage renal disease in all new patients receiving renal replacement therapy in New Zealand in 2010

Ethnicity	Diabetic nephropathy %	Glomerulonephritis %	Hypertension %
Māori	73.4	15.6	5.2
Pacific	68.9	17.9	4.7
Caucasian	24.6	25.6	21.1
Asian*	45.2	35.7	7.1
Total	**50.9**	**21.7**	**11.5**

***Asian patients included patients of Chinese, Malay, Indian and Vietnamese ethnicity.**

Mode of dialysis

2,378 patients were undergoing dialysis in NZ at the end of 2010. 36.5% of dialysis patients were Caucasian compared to 31.9% Māori, 22.8% Pacific and 8.5% Asian. 65% of dialysis patients were receiving haemodialysis (HD) compared to 35% receiving peritoneal dialysis (PD). 69% of new Māori patients commenced HD in 2010, compared to 31% commencing PD. 74% of new Pacific patients commenced HD, and 26% commenced PD.

Renal transplantation

At the end of 2010, there were 1,442 functioning renal transplants in NZ. Despite the much higher prevalence of ESRD in Māori and Pacific people, 77% of the patients with functioning renal transplants were Caucasian, compared to 9.6% Māori, 6.2% Pacific and 6.7% Asian patients. 110 renal transplant operations were performed in NZ in 2010, giving a transplant rate of 25 per million population per year. The median age for transplantation was 46.5 years. The rate of transplantation was highest among those under 14 years of age and a decline in rate correlated with older age. 64.5% of patients receiving a renal transplant in 2010 were Caucasian, 18.2% were Māori, 8.2% were Pacific and 7.3% were Asian. 4% of all dialysis patients and 5.1% of dialysis patients in the 15-64 year age group received a renal transplant in 2010. 10.6% of Caucasian

dialysis patients received a renal transplant, compared with 2.6% of Māori and 1.8% of Pacific dialysis patients.

At the end of 2010, the most common primary renal disease in all patients with functioning renal transplants was glomerulonephritis at 46.1%, compared to diabetes at 8.6% and hypertension at 4.2%. 45.1% of Caucasian patients with a functioning renal transplant had glomerulonephritis as their primary renal disease, compared to 42.8% of Māori, 58.4% of Pacific, and 51% of Asian patients. Diabetes was the primary disease in 6.3% of Caucasian patients with a functioning renal transplant, compared to 20.3% of Māori, 14.6% of Pacific and 12.5% of Asian patients.

Co-morbidities

Co-morbid conditions are common in patients with ESRD. The prevalence rates of the following co-morbidities include both confirmed and suspected cases.

Diabetes

Of the 503 new patients commencing RRT treatment in 2010, 56.1% had diabetes (4.3% type 1, 95.7% type 2). 31.7% of Caucasian patients had diabetes (15.9% type 1, 84.1% type 2) compared to 74.7% of Māori patients and 75.5% of Pacific patients (Māori – 1.7% type 1, 98.3% type 2, Pacific – 100% type 2). 52.4% of Asian patients had diabetes (100% type 2).

Coronary Artery Disease

The prevalence of established coronary artery disease in the total group of new patients was 38%, and was highest in the Māori patients at 42.9%, followed by 37.7% in the Pacific patients and 36.2% in the Caucasian patients.

Peripheral Vascular Disease

Peripheral vascular disease was reported in 19.7% of all new patients. The prevalence was highest in the Māori patients at 28.6% and the Pacific patients at 14.2%, compared to the Caucasian patients at 16.6%.

Cerebrovascular Disease

The prevalence of cerebrovascular disease was 12.5% in the total group, and was highest in the Māori patients at 15.6%, compared to the Pacific patients at 11.3%, and the Caucasian patients at 11.1%.

Chronic Lung Disease

Chronic lung disease was reported in 20.5% of the total group of new patients. Māori patients had the highest prevalence of chronic lung disease at 27.3%, compared to 20.8% in Pacific people and 18.1% in Caucasian patients.

Smoking

A positive smoking history was detected in 51.5% of all new patients (26.3% were current smokers, 73.7% were former smokers). The highest prevalence was seen in the Māori patients, where 70.1% had a positive smoking history (33.3% current smokers, 66.7% former smokers). The prevalence was less in the Pacific patients at 42.5% (24.4% current smokers, 75.6% former smokers), but not insignificant in the Caucasian patients, where nearly half (45.7%) were either current (18.7%) or former (81.3%) smokers.

Mortality

Of the 353 deaths in the ESRD population in 2010, 319 deaths were among the dialysis-dependent patients and 34 deaths were within the functioning transplant group. 45.1% of deaths in the dialysis-dependent patient group were attributed to cardiac disease, 21.3% were due to social reasons, 16.6% from infection, 9.7% from a vascular cause, 4.4% from a miscellaneous cause, and 2.5% from malignancy. The most common causes of death in the transplant group were malignancy (30.8%) and a cardiac event (23.5%). The most common cause of death for Māori and Pacific patients receiving RRT was attributed to a cardiac cause (49% and 50% respectively).

Table 3 illustrates the marked differences in death rates between patients being dialysed and patients with a functioning renal transplant, and also shows the impact diabetes has on the death rate in all modes of RRT.

Table 3: Death rate (per 100 patient years) in end-stage renal disease patients receiving renal replacement therapy in New Zealand in 2010

	Total	Diabetic	Non-diabetic
All Dialysis Patients	13.7	15.9	11.5
Functioning Transplant	1.4	3.6	0.9

Among deaths of females with ESRD receiving RRT in 2010 (*n*=149), 34.9% were Māori, compared to 43.6% Caucasian, 16.1% Pacific and 5.4% Asian. Among deaths of males with ESRD receiving RRT in 2010 (*n*=204), 30.4% were Māori, compared to 50.5% Caucasian, 12.8% Pacific and 5.9% Asian.

Late referrals (commencement of renal replacement therapy <3 months after referral)

In 2010, 19% of Māori patients were referred late for commencement of RRT. This was in comparison to 16% of Pacific patients and 15% of non-Indigenous patients.

The rate of progression to end-stage renal disease secondary to diabetic nephropathy in New Zealand Europeans compared to Māori and Pacific groups

Introduction

Higher rates of diabetic nephropathy are seen in Māori and Pacific patients, compared to the general population with diabetes in NZ, and these differences are noted at each stage of diabetic nephropathy. No systematic study looking at renal pathological changes in Māori and Pacific patients with diabetic nephropathy has been conducted, so there is uncertainty as to whether these groups follow the same pathological process of diabetic nephropathy as described in chapter 1.2.[63-65] A difference is seen in the rate of progression of diabetic nephropathy, which is notably more rapid in Māori and Pacific people.[109,110] In addition to this, morbidity rates associated with diabetic nephropathy are higher in Māori and Pacific patients in NZ, and mortality rates in Māori are amplified.[49,109] The human and economic cost of RRT in the ESRD population is high, and a sizeable portion of this cost is attributed to diabetic

nephropathy. The following section describes the differences in the prevalence, incidence and rate of progression of diabetic nephropathy in Māori and Pacific people, compared to NZ Europeans, and concludes with a summary on the estimated cost of ESRD treatment in NZ secondary to diabetic nephropathy, and its impact on the total costs of ESRD treatment.

Ethnic differences in the prevalence of diabetic nephropathy in New Zealand

One of the first studies in NZ to assess the prevalence of albuminuria between different ethnic groups with diabetes compared the rate of urinary albumin excretion (UAE) in 32 Māori, 34 Pacific and 66 NZ European patients with type 2 diabetes attending a Wellington diabetes clinic.[105] Differences in the urinary albumin to creatinine ratio (ACR) were observed between the different ethnic groups. The random urinary ACR was found to be higher in the Māori and Pacific patients compared to the NZ European patients (13.13, 12.00 and 2.79mg/mmol respectively, $p<0.05$). The correlation between hypertension and increased levels of albuminuria was noted to be stronger in the NZ European group compared to the Māori and Pacific patients, implying that BP alone was unlikely to account for the difference in UAE rates between the groups.

In the South Auckland Diabetes Survey,[111] the mean estimated daily UAE was notably higher in the Māori (94.8mg/day) and Pacific patients (44.2mg/day) compared to the NZ European patients (18.2mg/day). The respective prevalence of proteinuria (urinary albumin loss ≥300mg/24 hours) and ESRD was also greater in the Māori and Pacific patients. Differences in clinical characteristics were observed between the respective ethnic groups: the Māori and Pacific patients were younger at the age of diagnosis of diabetes, were more obese, and had worse glycaemic control than the NZ European patients (serum fructosamine - Māori 335 ± 78µmol/l, Pacific 367 ± 90µmol/l, NZ European 318 ± 55µmol/l, $p<0.001$). While mean systolic blood BP was found to be higher in the Māori patients compared to the NZ European patients (145 ± 31mmHg vs 141 ± 25mmHg), Pacific patients had the lowest mean systolic BP

(135 ± 25mmHg). The differences in albuminuria between the groups were evident at 5 years following the diagnosis of diabetes, demonstrating that nephropathy occurred earlier in the Māori and Pacific patients, and that an accelerated progression of renal disease was taking place, particularly in the Māori patients.

The "Te Wai O Rona" Study was a community-based diabetes intervention study which aimed to identify Māori either with diabetes or at risk of diabetes, and then facilitate community-based access to diabetes education, exercise and nutrition groups in an attempt to reduce the future incidence of diabetes in Māori communities.[112] The study provided new and important information on the prevalence of diabetic nephropathy among Māori subjects with newly diagnosed diabetes, finding a high prevalence of albuminuria (microalbuminuria/proteinuria) in 37.3% (29.6%/7.7%) of this group. After covariate adjustment, smoking was determined to be a risk factor for albuminuria, with an increased risk of 3.81(1.32-11.0)-fold in current smokers and 3.67(1.30-10.4)-fold in former smokers.

Ethnic differences in progression of diabetic nephropathy, morbidity and mortality

Rates of progression of diabetic nephropathy differ between Māori, Pacific and NZ European patients, and this was illustrated in a retrospective study comparing the rate of renal function decline during progression from chronic renal failure to ESRD in two groups: seventeen patients with ESRD secondary to type 1 diabetes (predominantly NZ European) were compared to twenty nine Māori and Pacific patients with ESRD secondary to type 2 diabetes.[110] A more rapid decline in GFR was noted in the patients with type 2 diabetes compared to those with type 1 diabetes (median GFR loss 1.7[1.2-2.3]ml/min/month vs 1.1[0.4-1.5]ml/min/month, p=0.017). The patients with type 1 diabetes were noted to have poorer glycaemic control than those with type 2 diabetes. Although a greater reduction in diastolic BP was observed in the patients with type 1 diabetes (8mmHg), after analysis of covariance, the differences in BP

between the groups were found to be non-significant, suggesting that the major determinant for the different rates of renal function decline was ethnicity.

A rapid progression of diabetic nephropathy to ESRD in Māori patients, in addition to higher rates of associated morbidity and mortality were seen in a recent study which compared the incidence of chronic renal failure, ESRD and renal mortality in Māori and NZ European patients with diabetes from a large cohort of patients, registered with the Waikato Regional Diabetes Service.[109] 7,900 patients with diabetes, free of renal complications (defined as a hospital admission for chronic renal disease, renal clinic attendance or contact with a home dialysis unit, commencement of dialysis, receipt of a renal transplant, or death from a renal cause) were retrospectively reviewed over a 4 year period. The incidence of RRT, rates of renal admission, and death from a renal cause were greater in the Māori patients. The respective increases in risk seen in the Māori group were 4-fold for renal death, 7-fold for renal admission, and with adjusted Hazard ratios, there was a 46-fold increase in the risk of dialysis or transplantation. The progression from CKD to ESRD was accelerated in the Māori patients. A high mortality risk from diabetes was also observed in a study looking at a cohort of 765 patients with diabetes, which showed that Māori were 2.66-fold more likely to die from a diabetes-related condition when compared to NZ Europeans, and had a 13.1-fold greater risk of death from nephropathy.[49] In this particular study, Pacific patients had a similar mortality rate to NZ Europeans.

Familial clustering and genetic predisposition to diabetic nephropathy

Familial clustering of diabetic nephropathy has been shown to occur,[89] and predisposition to renal disease in certain population groups around the world is well documented.[88] Subjects who have a first degree relative with renal disease have been shown to be at greater risk of developing renal disease themselves, in comparison to other subjects who do not have a positive family history of renal disease. These findings suggest that the development and progression of

nephropathy can be influenced by genetic factors in addition to environmental factors. There is evidence that Māori and Pacific people may have a familial predisposition to nephropathy. Thompson et al compared urinary albumin levels in subjects assigned to 4 groups:[113]

1. Subjects with a first degree relative (FDR) with diabetes and ESRD,
2. Subjects with a FDR with non-diabetic ESRD,
3. Subjects with a FDR with diabetes and no ESRD,
4. Subjects with no known relatives with ESRD or diabetes.

Māori and Pacific subjects who had a FDR with ESRD were found to have an increased urinary ACR compared to subjects without a FDR with ESRD. A family history of diabetes did not increase the risk for nephropathy. This implied that Māori and Pacific people may have a genetic susceptibility to renal disease per se rather than to diabetic nephropathy specifically.

The cost of renal replacement therapy

Diabetes, in its association with increased morbidity and mortality secondary to micro- and macrovascular disease, accounts for a substantial portion of the health budget in NZ.[114] An important study by Endre et al estimated the cost of ESRD secondary to diabetic nephropathy in NZ.[115] A cost-analysis was performed to estimate the direct healthcare costs and financial consequences of ESRD secondary to diabetic nephropathy, in comparison to the total annual costs associated with RRT (dialysis programmes and renal transplantation). The total annual costs of RRT and the costs attributable to ESRD were estimated for a single DHB, and costs were subsequently inferred to the whole of NZ to estimate the total national annual costs of RRT for the entire ESRD population in NZ. The annual costs of RRT and the costs attributable to ESRD secondary to diabetic nephropathy were extrapolated from the total annual costs. Based on the 2003 figures from the ANZDATA Registry,[116] the researchers calculated a conservative estimation of NZ$90 million as the total annual cost (annual dialysis costs [NZ$63 million] + renal transplantation costs [NZ$8 million] + other

CKD costs [including community pharmaceuticals, surgery for vascular access for dialysis and Tenckhoff catheter insertion] [NZ$8 million] + consultant time [NZ$5 million] + unassessed costs [NZ$6 million]). Diabetic nephropathy was the primary renal disease in 40% of the new patients commencing dialysis in 2003.[116] The estimated total annual cost for RRT secondary to diabetic nephropathy based on this percentage was NZ$36 million.[115] 55% of ESRD patients in NZ in 2003 had diabetes,[116] so the above cost is likely to be an underestimation of the true total cost of diabetic nephropathy in NZ. The researchers who conducted the above cost-analysis emphasised that other major costs, such as quality of life and the economic impact on families, work and leisure, were not included in this analysis.

Conclusion

High rates of diabetic nephropathy have been identified in Māori and Pacific people with diabetes. The rate of progression of renal disease is more rapid in these groups and they are at much higher risk of developing ESRD than NZ Europeans. The morbidity and mortality rates, particularly in Māori, are considerably higher than in NZ Europeans. The high prevalence of diabetes in Māori and Pacific people contributes to the high rates of diabetic nephropathy, but the higher prevalence rates of diabetic nephropathy in Māori and Pacific people are over and above the prevalence of diabetes, and become more apparent when compared to NZ Europeans with diabetes. The above findings from the ANZDATA 2011 report elucidate major differences between Māori, Pacific, Caucasian and Asian patients with ESRD in NZ. Māori and Pacific people are over-represented in the ESRD population. This is made more apparent when comparing the rates of new Māori and Pacific patients commencing RRT in 2010 with the NZ general population rates, in which Māori and Pacific people respectively comprise 14.6% and 6.9% of the NZ population, compared to a Caucasian population prevalence of 67.6%.[13] The high rates of diabetes in Māori and Pacific people contribute to diabetic nephropathy being the leading cause of ESRD in these two groups.

Renal transplant rates in Māori and Pacific people are low, and there is a notably low prevalence of diabetes as the primary renal disease in patients with functioning renal transplants. Of the 503 new patients commencing RRT in 2010, Māori had the highest prevalence rates for co-morbidities, aside from diabetes, where the Pacific group had the highest prevalence rate. Pacific patients had the second highest prevalence rates for coronary artery disease, cerebrovascular disease, and chronic lung disease. Death rates in Māori were comparatively higher, and this is no doubt influenced by Māori having the highest prevalence rates for each co-morbidity. In addition, as a consequence of high tobacco use, Māori have increased morbidity and mortality rates.[117] A study looking at mortality rates in ESRD patients receiving PD in NZ demonstrated an increase in mortality in patients who had a positive history of smoking compared to non-smokers, and mortality was further increased if the patient also had diabetes.[118] Late referral rates shown here are also higher in Māori patients.

While further research is needed to identify inherent factors that may predispose Māori and Pacific people to renal disease, finding effective ways to prevent diabetes, and to prevent the onset and delay the progression of diabetic nephropathy to ESRD in Māori and Pacific people in NZ is crucial.

1.4 The impact of blood pressure control on slowing the progression of renal disease in diabetic nephropathy

Introduction

The importance of good blood pressure (BP) control in preventing and managing patients with diabetic nephropathy was demonstrated in the early 1980s by Parving et al, where a 57% reduction in loss of glomerular filtration rate (GFR) was achieved in patients with type 1 diabetes by decreasing the average BP from 144/97mmHg to 128/84mmHg, through the use of a diuretic, beta blocker or vasodilating agent.[119] The United Kingdom Prospective Diabetes Study (UKPDS) went on to demonstrate a benefit in achieving good BP control in patients with type 2 diabetes, showing that this could lead to a reduction in the risk of diabetes complications.[78] With each 10mmHg reduction in systolic BP, a 13% reduction in risk of microvascular complications (p<0.0001) occurred, and the lowest risk was associated with a systolic BP <120mmHg.

The discovery and subsequent proven efficacy of agents that block the renin-angiotensin-aldosterone system (RAAS) has revolutionised the treatment of diabetic nephropathy, by decreasing the risk of progression from microalbuminuria to macroalbuminuria, and by delaying renal function decline. Other agents have also proven effective in offering renoprotection in diabetic nephropathy. The following review summarises the findings of randomised controlled trials (RCT) that have looked at the effect of antihypertensive agents on BP control, and their effects on achieving improved renal outcomes in patients predominantly with type 2 diabetes, either secondary to good BP control, or as in the case of many studies, achieving these outcomes independent of BP.

Search Strategy

A literature search was performed on the electronic databases OVID Medline®, PubMed, ScienceDirect, and other university library resources including E-journals for studies from peer-reviewed journals, supporting the efficacy of

good BP control on slowing the progression of renal disease in diabetic nephropathy. Search terms used included 'randomised controlled trials, hypertension, diabetic nephropathy, microalbuminuria, macroalbuminuria, proteinuria, type 2 diabetes, renin-angiotensin-aldosterone system, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, renoprotection, glomerular filtration rate, dialysis, and end-stage renal disease'.

Angiotensin converting enzyme inhibitor versus placebo

The beneficial effect of angiotensin converting enzyme (ACE) inhibitors in patients with nephropathy secondary to diabetes was demonstrated in a landmark RCT examining the effects of these agents on delaying progression of renal disease in patients with type 1 diabetes and proteinuria (defined as a urinary protein loss >500g/24 hours), independent on their effect on BP.[120] In this 3-year study, 409 patients were randomised to receive either captopril or placebo. The target BP goal was <140/90mmHg. A 48% risk reduction in the primary endpoint (a doubling of the baseline serum creatinine) was seen in the captopril group, in addition to a 50% risk reduction in the combined endpoints of dialysis, transplantation and death. Captopril patients with a higher baseline serum creatinine (177µmol/l) achieved a greater risk reduction than the respective patient groups with a serum creatinine of 155µmol/l and 88.4µmol/l (risk reduction 76% vs 55% vs 17%). Follow-up BP was similar in both groups. The study determined that ACE inhibition was more effective than BP control alone in slowing the progression of diabetic nephropathy secondary to type 1 diabetes.

The Microalbuminuria, Cardiovascular (CV) and Renal Outcomes-Heart Outcomes Prevention Evaluation (MICRO-HOPE) study was a sub-study of the HOPE study which examined the effect of once daily ramipril 10mg on the risk of developing overt nephropathy in patients with high-risk diabetes (both type 1 or type 2).[94] The ramipril group achieved a BP reduction of 2.5mmHg systolic, and 1mmHg diastolic. When corrected for BP, reductions in the risk of CV morbidity

and mortality were seen in addition to a reduction in stroke risk. A 24% relative risk (RR) reduction in the progression of diabetic nephropathy was also seen, but this was not adjusted for the change in BP. The Action in Diabetes and Vascular Disease: Preterax (perindopril/indapamide) and Diamicron MR (gliclazide) Controlled Evaluation (ADVANCE) trial was a multi-centre RCT that compared the effects of a fixed combination of the ACE inhibitor perindopril and indapamide, a diuretic, to placebo on micro- and macrovascular outcomes in patients with type 2 diabetes.[121] The primary endpoints were composites of major micro- and macrovascular events, including new or worsening renal or diabetic eye disease, CV death, non-fatal stroke, and non-fatal myocardial infarction. 11,140 patients were randomised to receive the perindopril/indapamide combination or placebo. The mean follow-up was 4.3 years. A 9% reduction in RR was seen for major micro- or macrovascular events in the perindopril/indapamide group. The RR of CV death was reduced by 18% and there was a 14% RR reduction in death from any cause in the active treatment group. A reduction in mean BP (5.6/2.2mmHg) was seen in this group in addition to reductions in the rate of new onset microalbuminuria (19.6% vs 23.6%), and in the combined endpoint of worsening or new onset microalbuminuria or proteinuria.

Angiotensin receptor blocker versus placebo

The angiotensin receptor blockers (ARB) have been studied more extensively in large RCTs than ACE inhibitors in evaluating their renoprotective effects in patients with type 2 diabetes and diabetic nephropathy. The following studies helped confirm the efficacy of ARBs in reducing the progression of albuminuria and GFR decline in this patient population.

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) study group conducted a multi-national, randomised, double-blind, placebo-controlled study, evaluating the effectiveness of the ARB irbesartan in delaying the progression of diabetic nephropathy in 590 patients with type 2 diabetes

and microalbuminuria.[122] The irbesartan group received either once daily irbesartan 150mg or 300mg. Folllow-up was for 2 years. The primary outcome was the time to onset of diabetic nephropathy (defined as a (urinary albumin excretion (UAE) rate >200µg/minute, or greater than 30% above baseline level, and persistent overnight albuminuria). By the end of the study, the UAE level was reduced by 38% with 300mg irbesartan compared to 24% with 150mg and 2% with placebo. Notably, a greater reduction in UAE level was seen with 300mg irbesartan compared with 150mg. By the final study visit, restoration of normoalbuminuria was more frequent with 300mg irbesartan than the other two groups. Adjusted Hazard ratios for reaching the primary endpoint were 0.56 in the 150mg group (95% confidence interval 0.31-0.99; p=0.05) and 0.32 in the 300mg group (95% confidence interval 0.15-0.65; p<0.001). No difference was seen between the 3 groups in the initial or sustained (3 to 24 months) rate in decline of creatinine clearance. BP remained similar in all groups throughout the study. Not only was irbesartan shown to be superior to placebo, but the 300mg dose showed greater renoprotective efficacy than the 150mg dose.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) was another large RCT which saw 1513 patients with type 2 diabetes and diabetic nephropathy (mean serum creatinine 168µmol/l) randomly assigned to losartan 100mg daily or placebo, in addition to their conventional antihypertensive therapy (with the exclusion of ACE inhibitors).[123] Follow-up was for a mean of 3.4 years. The composite primary endpoint was a doubling of baseline serum creatinine, development of end-stage renal disease (ESRD) or death. Proteinuria, rate of progression of renal disease, and CV morbidity and mortality comprised the composite secondary endpoints. Compared to placebo, losartan reduced the risk of reaching the primary endpoint by 16% (p=0.02). The respective incidence of a doubling of the serum creatinine and reaching ESRD was reduced by 25% (p=0.006) and 28% (p=0.002) in the losartan group. The level of proteinuria decreased by 35% (p<0.001) in the losartan group. No difference was seen between the groups in death rate.

The rate for first hospitalisation for heart failure was reduced in the losartan group by 32% (p=0.005), but there were no other significant differences in regard to CV morbidity and mortality. Post-hoc analysis of the RENAAL study showed that within all categories of attained BP, a greater decrease in albuminuria was associated with a progressively lower risk of ESRD.[124] An 18% reduction in CV risk was seen for every 50% decrease in the UAE rate. Also, the risk of ESRD or death was increased by 6.7% for every 10mmHg increase in the baseline systolic BP. The most significant risk factor for progression on renal disease was the degree of proteinuria, at baseline and following 6 months of therapy.

Angiotensin receptor blocker versus dihydropiridine calcium channel antagonist

The superiority of ARBs over dihydropyridine calcium channel antagonists in the treatment of diabetic nephropathy in type 2 diabetes was demonstrated in the Irbesartan Diabetic Nephropathy Trial (IDNT), a randomised, placebo-controlled study of 1715 patients with type 2 diabetes and diabetic nephropathy.[125] Once daily irbesartan 300mg was compared to the calcium channel antagonist amlodipine 10mg and placebo, to evaluate their effectiveness at slowing the progression of renal disease, independent of their capacity to reduce BP. All patients had proteinuria, with a minimum urinary protein loss of 900mg/24 hours. The mean serum creatinine was 150µmol/l. The target BP was ≤135/85 mmHg. The primary composite endpoint was a doubling of the baseline serum creatinine, the development of ESRD, or death from any cause. The secondary endpoint was the time to a CV outcome. After a mean follow-up of 2.6 years, the composite endpoint was reduced in the irbesartan group by 20% compared to the placebo group and by 23% compared to the amlodipine group. A risk reduction was also seen in the irbesartan group for doubling of the serum creatinine (33% lower than placebo [p=0.003], and 37% lower than amlodipine [p<0.001]). The RR was reduced by 23% and trended towards significance for reaching ESRD in the irbesartan group compared to the other groups (p=0.07).

The rate of increase in serum creatinine was also lower in the irbesartan group. Renal outcomes were optimal with a systolic BP <134mmHg. No difference was seen in BP between the irbesartan and the amlodipine group. A difference in mean arterial pressure (MAP) was seen between the irbesartan and placebo group, but after adjustment for this, the differences in endpoints between these two groups remained significant.

Angiotensin converting enzyme inhibitors versus angiotensin receptor blockers

There is a paucity of head to head comparative studies evaluating the renoprotective effect of ACE inhibitors versus ARBs in patients with type 2 diabetes and nephropathy. However, those studies that have examined this question have shown similarities in the efficacy of both drug families to delay the progression of diabetic nephropathy.

A one-year, multi-centre, RCT compared enalapril to losartan to examine the effects of each drug on albuminuria and renal function in relation to clinic and ambulatory BP in patients with type 2 diabetes, hypertension and early nephropathy.[126] Reductions were seen in clinic BP and ambulatory BP in both groups, but no difference in BP was seen between the groups. A correlation between changes in systolic and diastolic ambulatory BP and a reduction in UAE over the one-year study duration was noted in both groups. The same correlation was not seen between the decrease in UAE and clinic BP. An overall decline in GFR by approximately 9% was seen in both groups, with a plateauing of the GFR by the end of the study.

Another comparative head to head study was a multi-centre, double-blind, RCT that compared enalapril to telmisartan in 250 patients with type 2 diabetes and early nephropathy in a 5-year study.[127] Patients received either once daily enalapril 20mg or telmisartan 80mg. The primary endpoint was a change in GFR from baseline to the last available value. Secondary endpoints included annual changes in serum creatinine, GFR, UAE, and BP. Respective ESRD, CV event and

death rates were also examined. After 5 years, the mean GFR loss in the telmisartan group was 17.9ml/min/1.73m^2 compared to 14.9ml/min/1.73m^2 in the enalapril group, a non-significant difference. Also, there were no differences between the groups in the secondary endpoints, in particular, no differences in the risk of CV events.

Angiotensin converting enzyme inhibitor versus angiotensin receptor blocker versus combination therapy

Dual blockade of the RAAS, affecting both the ACE and the angiotensin II receptor has been shown to be effective in lowering BP and a number of studies[128-130] have shown its efficacy in reducing UAE over and above the effects of either agent used as monotherapy. However, the combination of these agents has been shown to be associated with an increase in adverse effects,[131] as described below in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study.

One of the first RCTs to purport the effects of combination therapy was the Candesartan and Lisinopril Microalbuminuria (CALM) Study, which compared an ARB with both an ACE inhibitor and their combination on BP and UAE in 199 patients with type 2 diabetes and hypertension.[128] Patients received either once daily candesartan 16mg or lisinopril 20mg for 12 weeks, followed by either 12 weeks of monotherapy or a combination of both agents. Reductions in diastolic BP and UAE in the first 12 weeks were similar in the two monotherapy groups. In the second 12 weeks, the combination group achieved greater reductions in diastolic BP and UAE than the monotherapy groups. However, evidence from the much larger ONTARGET study forced a re-think about dual blockade therapy. The ONTARGET study was a large multi-centre double-blind study that compared the effect of telmisartan, ramipril, or a combination of both to reduce CV morbidity and mortality in patients who had established atherosclerotic vascular disease, or diabetes with evidence of end-organ damage.[131] 25,620 patients underwent randomisation to receive once daily telmisartan 80 mg,

once daily ramipril 10 mg, or a combination of both. 38% of patients had diabetes. 85% of patients had known CV disease and 69% had hypertension. The primary composite outcome was death from CV causes, myocardial infarction, stroke, hospitalisation, or heart failure. The primary renal outcome was a composite of dialysis, doubling of serum creatinine and death. The median duration of follow-up was 56 months. There was no difference between the 3 groups in the occurrence of the primary outcome. While the increase in UAE was less with telmisartan combination-therapy, the doubling of serum creatinine was more frequent with combination-therapy. Hyperkalaemia was also more frequent with combination-therapy. Hypotensive symptoms and syncope were also increased with combination-therapy.

Aldosterone antagonists

Aldosterone antagonists, in addition to usual antihypertensive treatment, have been shown to reduce BP and add further renoprotective benefit to patients with type 1 diabetes and nephropathy.[132] RCTs have also been conducted to evaluate the effect of aldosterone antagonists alone or in combination with other antihypertensive agents.

One RCT evaluated the effects of spironolactone, cilazapril and their combination on albuminuria.[133] 60 female patients with type 2 diabetes and nephropathy underwent randomisation to receive either once daily spironolactone 100mg or once daily cilazapril 5mg for 24 weeks, and then both groups received a combination of once daily spironolactone 50mg + cilazapril 2.5mg for a further 24 weeks. A greater reduction in albuminuria occurred in the spironolactone group compared to the cilazapril group (p=0.002), and the combined treatment resulted in only a moderate improvement in albuminuria. Hyperkalaemia affected 15% of patients during the second 24 weeks when the combination of spironolactone and cilazapril was used.

Another study randomised 21 patients with type 2 diabetes and nephropathy to receive either spironolactone 25 mg daily or placebo in addition to antihypertensive treatment including diuretics and maximally recommended doses of an ACE inhibitor and/or an ARB.[134] The addition of spironolactone resulted in a reduction in albuminuria (by 33%) and a reduction in systolic and diastolic BP. A further RCT compared the addition of either losartan or spironolactone to lisinopril in 81 patients with type 2 diabetes and albuminuria.[135] Follow-up was for 48 weeks. Compared to placebo, the lisinopril/spironolactone combination reduced the urinary ACR by 34%, which was greater than the 16.8% reduction in the lisinopril/losartan group. However, both of these groups experienced higher levels of serum potassium than the placebo group.

Other agents

In regard to the renoprotective efficacy of other antihypertensive agents, there is evidence that the non-dihydropyridine calcium channel antagonists are effective in delaying the progression of diabetic nephropathy in type 2 diabetes.

One study compared the renoprotective effects of an ACE inhibitor to two non-dihydropyridine calcium channel antagonists and a beta blocker in 52 patients with type 2 diabetes, hypertension and diabetic nephropathy.[136] Patients were randomised to receive either once daily lisinopril 51 ± 9mg, twice daily verapamil 205 ± 16mg, once daily diltiazem SR 212 ± 19mg, or once daily atenolol 86 ± 9mg. Patients were followed up for 6 years. The reduction in mean arterial pressure over the study period was similar between the 4 groups, but there was a greater decline in GFR with atenolol compared to the other 3 groups. The mean reduction in proteinuria levels was similar with lisinopril and the calcium channel antagonists, but was less in the atenolol group.

Target blood pressure levels in patients with diabetes

Numerous studies have examined the optimal target BP level, aiming for the greatest possible reduction in CV risk, coupled with the lowest possible incidence of adverse effects secondary to antihypertensive therapy. The Hypertension Optimal Treatment (HOT) study showed an improvement in CV outcomes, particularly in the prevention of stroke, in patients achieving a diastolic BP of 82.6 mmHg.[137] The UKPDS demonstrated that better BP control (achieving a mean BP of 144/82mmHg) was associated with a reduction in diabetes-related deaths, stroke, and microvascular endpoints, compared with the group assigned to less tight BP control (mean BP 154/87mmHg, $p<0.0001$).[138] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP study group investigated whether therapy targeting BP control <120mmHg systolic would reduce the risk of major CV events in high-risk patients with type 2 diabetes.[139] 4733 subjects were randomly assigned to either intensive BP control (aiming for a systolic BP <120mmHg), or to standard therapy (aiming for a systolic BP <140mmHg). The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke or death from a CV cause. The study had a mean follow-up duration of 4.7 years. At the end of the study, there was no difference between the groups in occurrence rate of the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes. The annual rates of stroke, a secondary outcome, were higher in the group receiving standard therapy. The intensive therapy group had a higher rate of adverse events attributed to the antihypertensive therapy, compared to the standard group. The respective incidence rates of hypokalaemia, and of an estimated GFR below 30ml/min/1.73m^2 was higher in the intensive therapy group. Serious adverse event rates secondary to hyperkalaemia were also higher in this group. There was no difference between the groups in the frequency of ESRD or the need for dialysis. The incidence of macroalbuminuria was lower in the intensive therapy group but there was no difference in the incidence of microalbuminuria.

The current NKF KDOQI™ Guidelines,[66] the American Diabetes Association (ADA) Standards of Medical Care in Diabetes,[140] and The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[141] all recommend a target BP of <130/80mmHg in all patients with diabetes with or without evidence of CKD, which do not reflect the outcomes of the ACCORD study.

Conclusion

The evidence is clear that good BP control, achieved through the use of antihypertensive agents, can delay the progression of albuminuria and renal function decline in patients with diabetic nephropathy. The studies summarised above show that ACE inhibitors and ARBs are both effective in reducing albuminuria, and slowing the progression of renal function decline in patients with type 2 diabetes and diabetic nephropathy, independent of BP. Superiority of ARBs over the dihydropyridine calcium channel antagonists is demonstrated, but there is a lack of studies comparing ARBs to the non-dihydropyridine calcium channel antagonists. The use of dual blockade (ACE inhibitor/ARB combination) dissipated after the results of the ONTARGET study were revealed. The aldosterone antagonists, although associated with a higher risk of hyperkalaemia, have demonstrated promising results in the above RCTs, implying that cautious use of these drugs in diabetic nephropathy may be very beneficial. The pharmacological evidence is clear on which agents to use and in what doses, to help prevent and delay diabetic nephropathy in patients with type 2 diabetes and diabetic nephropathy. The ACCORD BP study, however, has raised questions about the BP targets that have previously been accepted and promoted by guideline groups. The next hurdle that arises is the question of how this evidence-based therapy can be effectively delivered to our patient population with diabetes and diabetic nephropathy, where traditional methods of healthcare delivery have achieved sub-optimal success rates.

Chapter 2

2.1 Approaches to blood pressure control in the community

Introduction

Hypertension is one of the most common non-communicable conditions seen in the general population, and is a major risk factor for cardiovascular (CV) and renal disease.[142] Its prevalence is highest in the aging population, and it is also common in population groups with high prevalence rates of diabetes and obesity.[78,142] As the aging population grows, and the prevalence rates of diabetes and obesity increase, the proportion of people with hypertension is also likely to increase, which will result in an increase in rates of CV and stroke morbidity and mortality, and chronic kidney disease (CKD).

In the most recent New Zealand Health Survey (NZHS)-2006/2007, one in seven adults in NZ reported taking medication for elevated blood pressure (BP) (13.6% [13.0-14.3%]).[18] This is an underestimation of the true prevalence of hypertension in the NZ population, as it did not include people with undiagnosed or un-medicated hypertension.

The development of effective and inexpensive antihypertensive medications in the last few decades has revolutionised the treatment of hypertension on a global scale. Randomised controlled trials (RCT) have examined the effectiveness of antihypertensive medication on BP control and its resultant effect on short and long-term renal and CV outcomes and have shown that treatment of hypertension can lead to significant risk reductions in renal outcomes and CV morbidity and mortality.[94,119,120,122,123]

Despite overwhelming evidence to show that good BP control in population groups with hypertension and diabetes can delay the progression of both microvascular and macrovascular disease, studies have demonstrated that effective management of BP is not widely achieved in everyday practice, resulting in inadequately controlled BP in the majority of the hypertensive

population.[143-145] In an analysis of National Health and Nutrition Examination Survey (NHANES) data, in which 28.7% of participants had hypertension, only 31% of those patients had controlled hypertension.[146] The following literature review discusses the factors that contribute to the low rates of controlled hypertension, and potential measures to overcome them. Other approaches to BP control are also discussed.

Search strategy

A literature search was performed on the electronic databases OVID Medline®, PubMed, ScienceDirect, the Cochrane database and other university library resources including E-journals for studies from peer-reviewed journals that looked at approaches to BP control in the community. Search terms used included 'hypertension, blood pressure control, clinical inertia, intervention, community, nurse-led care, pharmacist-led care, community healthcare workers, healthcare assistants, education'.

Factors contributing to inadequate blood pressure control

The traditional model of care for hypertension management has involved direct physician-patient encounters in the clinic setting, where the BP is measured and antihypertensive medication is prescribed at the discretion of the treating physician.[147] The low rates of well controlled BP in the general population imply that the traditional model fails to adequately address the needs of the community. Undoubtedly, there are several contributing factors to this. One term that encompasses many of these factors is clinical inertia, or therapeutic inertia, defined as a lack of treatment intensification in a patient not at evidence-based goals for care.[148,149] Three principal factors which can result in clinical inertia have been proposed - physician factors, patient factors, and system or practice factors.[148,149] Physician factors include inadequate education and training in how to attain therapeutic goals, and a lack of familiarity and knowledge of the recommended international and national guidelines for the treatment of hypertension, which can respectively lead to unclear goal setting

of health targets. Other factors include a tendency to accept a BP above the recommended target range, failure to initiate and titrate treatment until treatment goals are achieved, and an overestimation of the care provided.[150] The results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP study, which showed that achieving tight BP control (mean systolic BP 119.3mmHg) in patients with diabetes did not accrue greater risk reduction of composite CV outcomes, but increased the risk of adverse events, introduced further uncertainty for clinicians as to what therapeutic targets of BP control to aim for.[139] Additional physician factors include the use of 'soft' reasons to justify lack of treatment intensification, such as attributing a high BP reading to the patient "rushing to the appointment" and consequently choosing not to escalate therapy. Failure to identify and manage co-morbid conditions such as depression, and adopting a reactive approach instead of a proactive one in treating chronic disease also contribute to clinical inertia. Further factors include limited health resources, and budget and time constraints which result in heavy workloads for clinicians and high patient to doctor ratios.

Patient factors include denial having the disease, a lack of symptoms and poor health literacy, resulting in a limited understanding of the importance of good BP control, and the frequent need for polypharmacy. Financial and transport issues preventing patients from regular clinic attendance and the cost of filling medication prescriptions present further barriers to attaining good BP control.[143,145,151] Medication side effects, a lack of communication with and trust of healthcare professionals, depression, and resistance to adopting lifestyle modifications that will enhance chronic care are other important patient factors, all of which can lead to non-adherence of medications. Also, compliance with antihypertensive medication use is difficult to monitor and measure. The difficulty in identifying the compliant patient can result in reluctance by physicians to complicate an antihypertensive regimen by adding more agents, putting the patient at greater risk of experiencing drug side effects and a greater likelihood of non-compliance.[145]

System factors include inadequate patient recall systems, limited regular or frequent follow-up for monitoring of BP, a lack of active outreach services, and suboptimal communication between practice staff and other healthcare providers involved in the patient's care. All of these factors can contribute to the decreased likelihood of optimisation of antihypertensive agents.[151]

Measures to overcome clinical inertia

A number of measures to overcome clinical inertia have been proposed. Ways to address physician factors include monitoring quality of care and provision of feedback on specific clinical outcomes to physicians involved in BP control, attaining consensus on which therapeutic guidelines to follow, utilising protocol-based care for BP management, and placing more emphasis on physician accountability.[148,149] An example of this is where the physician has to document a reason for therapy not being intensified in a patient who has not reached therapeutic BP targets.[148,149]

For patient factors, more frequent visits with the physician can lead to an increase in familiarity and trust between doctor and patient, and a greater understanding by the patient of what intensified care means, and that it should not be seen as 'failed therapy.' Given that clinic, transport, and medication costs are factors that reduce access to healthcare, an effective intervention needs to be affordable to patients. Measures to overcome system factors include the use of recall systems which enable planned and timed clinic visits for intensification of therapy, followed by a return to less frequent clinic visits once the patient has reached therapeutic goals. The benefits of planned visits include having a greater opportunity to intensify treatment, leading to a more rapid titration of treatment to reach therapeutic goals, and an increase in familiarity and trust between physician and patient.

Interventions to improve blood pressure control in the community

In addition to adopting measures to overcome the factors that contribute to clinical inertia, there is an imperative to find innovative methods of healthcare

delivery that will lead to effective BP control. The potential benefits of other healthcare delivery models may include improved access for patients to healthcare services, improved treatment intensification leading to a greater likelihood of attaining therapeutic goals, increased patient participation and compliance, and cost-savings. The optimal delivery of healthcare in terms of BP control has been sought by many, and numerous interventions to improve BP control have been studied. The following summary explores these interventions.

Self-monitoring of blood pressure

Self-monitoring of BP is an approach to the management of hypertension in the community that has gained much popularity with patients.[152] Self-monitoring involves measuring one's own BP outside the clinic setting (usually at home or in the workplace). Given the wide daily variation in an individual's BP, an advantage of self-monitoring over clinic BP is that it allows for multiple and frequent BP measurements, resulting in a more accurate estimation of the average BP, in comparison to the infrequent BP readings obtained at clinic visits.[152,153] This can be particularly useful in assessing BP response during the titration of antihypertensive medications. Self-monitoring of BP can help distinguish sustained hypertension from "white coat" hypertension, where in the latter, clinic BP is elevated and home BP readings are in the normal range.[152,153] This is also the case with the diagnosis of masked hypertension, where clinic BP is in the normal range but home readings are persistently elevated.[152,153] There is evidence that self-monitoring better predicts long-term CV outcome than clinic BP.[154] With regard to cost-effectiveness, one RCT found that the cost-effectiveness of self-monitoring versus clinic BP in 441 patients was similar.[155]

Self-monitoring may lead to better medication compliance, due to patients having the opportunity to take greater participation in their own healthcare.[156] The effectiveness of self-monitoring of BP can be increased by combining it with

another intervention. A combination of nurse-led hypertension management and self-monitoring of BP can be more effective than the traditional model of care provided by a primary care physician.[157,158] In a study evaluating the effect of nurse-managed hypertension via telemonitoring of patients' self-monitored BP results, frequent and regular contact between patient and nurse, with regular review of the self-monitored BP results, and counseling on lifestyle modification and medication adherence in accordance with national guidelines led to a reduction in systolic BP (-13.0mmHg in the intervention group vs -7.5mmHg in the conventional group, p=0.04).[157]

Nurse-led care

The concept of nurse-led hypertension clinics has gained popularity over the last few decades and studies have identified several factors that give this model of care advantage over the traditional model, where physicians have operated as the primary healthcare providers, clinical decision-makers and medication prescribers. Regular and frequent patient follow-up, outreach clinics in the workplace,[159] authorisation of nurses to adjust antihypertensive regimens, and strict adherence by nurses to stepwise treatment algorithms based on recommended BP guidelines have not only led to improved BP control,[147] but in one study a reduction in future risk of CV disease and stroke in patients with type 2 diabetes, hypertension and albuminuria was demonstrated.[160] Longer consultation times in nurse-led clinics have been shown to increase patient satisfaction.[161] The clinical inertia associated with the traditional model of care is less likely to occur in nurse-led clinics, due to greater adherence by nurses to stepwise treatment algorithms and protocol-driven systems.[162]

An important point to note is that the effectiveness of the nurse-led model of care is dependent on the study intervention allowing nurses to implement changes to a patient's medication regimen, by dose adjustment, or by prescribing new antihypertensive agents. Oakeshott's review of ten studies examining nurse-led hypertension care and CV health promotion,[162] and a

review of nurse-led hypertension care by Clark[147] have shown that if the intervention does not involve a change in prescribing, then there is little or no effect on BP. A model of care involving nurse-led antihypertensive medication adherence support has been examined, where patients attended clinic sessions with a nurse, and were given the opportunity to discuss any problems encountered with their antihypertensive medication (for example, side effects, lack of understanding of the reason for their medication, and non-acceptability to take prescribed medication).[163] Nurses then had the opportunity to educate patients and strategise ways to facilitate their medication compliance. This did not include any change to the patient's medication regimen. This model of care was not shown to be any better than usual care, and was more expensive. The nurse-led model of care is described in further detail in chapter 2.2.

Pharmacist-led care

A number of studies have evaluated the effect of pharmacist-led care in the management of BP control in the community. In these studies, the intervention groups have attended frequent clinic visits with a pharmacist (monthly to bi-monthly), and have undergone BP monitoring (with or without nursing staff assistance). The pharmacist has then provided drug counseling and medication adherence aids to the patient, and has implemented changes to the patient's antihypertensive regimen either directly, by a pre-arranged authorisation to implement medication changes in accordance with a stepwise treatment protocol based on recommended BP guidelines, or as in most cases, indirectly, with the pharmacist making treatment recommendations to the patient's primary care physician (either by a face-to-face encounter, fax, email or post) after clinic review of the patient.[164-171] The control groups in these studies have received standard care from their primary care physicians. This type of intervention has been associated with a greater reduction in systolic and diastolic BP compared to control groups. This was demonstrated in a study in which 179 subjects with uncontrolled hypertension were randomised to either an intervention group who received their BP care from a collaborative

pharmacist-physician team, or to usual care.[166] Follow-up duration was 9 months. Subjects in the intervention group were seen 2 monthly for 8 months. The pharmacist reviewed BP levels, and if above target range (>130/80mmHg in subject with diabetes or CKD, >140/90mmHg for all other subjects), a face-to-face recommendation of antihypertensive regimen adjustment was made to the physician. At the end of the study, BP was controlled in 89.1% of the intervention group, compared to 52.9% of the usual care group (adjusted odds ratio 8.9, 95% CI 3.8-20.7, p<0.001). The mean adjusted difference in systolic BP was 8.7mmHg (95% CI 4.4-12.9), and the diastolic difference was 5.4mmHg (95% CI 2.8-8.0). The mean number of antihypertensive agents was higher in the intervention group compared to the usual care group (intervention care 2.4±0.9 vs usual care 1.9 ± 1.0, p=0.003). Comparable to the findings from the studies of nurse-led hypertension clinics, frequent clinic visits by the pharmacist with direct or indirect antihypertensive medication adjustment in adherence to treatment protocols based on BP guidelines are associated with the increased effectiveness of this intervention.

Community healthcare workers

Few studies have looked at the effectiveness of community healthcare workers in the management of hypertension in the community. One study evaluated the effectiveness of enhanced tracking and follow-up services provided by lay healthcare workers in promoting medical follow-up of patients diagnosed with hypertension at urban community sites. The intervention group was more likely to undergo medical follow-up for BP management than the control group.[172] Another study examined the effectiveness of an educational-behavioural-pharmacologic intervention by a community healthcare worker-nurse-physician team on BP control, progression of left ventricular hypertrophy (LVH) and renal insufficiency in 309 patients with hypertension, from a low socioeconomic population group.[173] Follow-up was for 3 years. Patients randomised to the intervention group attended regular nurse-led clinic visits, where treatment was intensified in adherence with a protocol based on national hypertension

treatment guidelines. The community healthcare worker visited the patient at home at least once a year during the study, providing referrals to social services, and assisting with housing issues. The intervention group achieved significantly lower systolic and diastolic BP, a decreased progression of LVH, and a trend towards a delay in progressive renal function decline. This study is discussed in more detail in chapter 2.2.

Organisational interventions

The need for robust systems that guarantee appropriate recall and regular follow-up of patients in general practice and community based clinics is clear. An organisational intervention was implemented in the Hypertension Detection Follow-Up Programme, a multifaceted RCT of 10,940 patients, conducted more than 30 years ago.[174] The study intervention involved a combination of several different strategies, including a system of patient registration and an organised system of patient recall and regular review, in conjunction with a vigorous stepped care approach to antihypertensive medication treatment. This led to a significant reduction in systolic and diastolic BP in the intervention group, and 5-year mortality from all causes was significantly lower in this group compared to the control group.[175]

Effectiveness of interventions to reduce blood pressure

A systematic review performed by the Cochrane Group looked at the effectiveness of a range of interventions whose objective was to improve both follow-up and BP control in patients taking antihypertensive medications.[176] Different models of care from 72 RCTs were reviewed, and included self-monitoring of BP, educational interventions, directed either at the patient or at healthcare professionals, nurse-led care, pharmacist-led care, and organisational interventions aiming to improve the delivery of care.

The most effective model of care for improving BP control was that seen in the Hypertension Detection Follow-Up Programme, described above,[175] demonstrating significant improvement in BP control and lower 5-year all-cause

mortality rates in the intervention group. The other interventions had variable results in regard to effectiveness. Self-monitoring of BP was associated with moderate net reductions in systolic and diastolic BP. The majority of nurse-led and pharmacist-led interventions were associated with an improvement in BP control, but the review emphasised the need for further evaluation in these models of care. Educational interventions alone did not result in significant net reductions in BP. Of note, the Cochrane report did not include any studies involving community healthcare workers.

Conclusion

Common features are evident in all of the interventions shown to be effective in improving BP control in the community. These features include having a clear set of treatment goals, having well-trained healthcare professionals who are proficient in treatment intensification, utilising stepwise algorithms to facilitate change in an antihypertensive medication regimen if target BP is not met, having a robust system of patient registration and recall coupled with regular and frequent patient follow-up visits for BP monitoring and review of medications, having greater access to outreach services, and having affordable services to patients in relation to clinic, transport and medication costs.

2.2 Comparison of nurse-led hypertension clinics to primary care follow-up and associated macrovascular and renal outcomes

Introduction

There is an increasing need to find models of healthcare delivery that will result in effective blood pressure (BP) control in the community. A number of important factors have already been identified as cardinal to any intervention striving to attain this objective. These include a robust system of patient registration and recall in conjunction with regular and frequent follow-up of patients, and adjustments to antihypertensive medication regimens using a stepped-care approach, in strict adherence to recommended hypertension treatment guidelines, if target BP levels are not met.[176]

As discussed in chapter 2.1, the effectiveness of the nurse-led model of care is critically dependent on the study intervention allowing nurses to initiate changes to a patient's medication regimen, either by physician or nurse adjustment of doses of existing medications, and prescription of new antihypertensive agents, in accordance with BP guidelines. If the intervention does not involve nurse-initiated medication changes when the target BP is not met, then there is little or no effect on BP.[147,162] If this model of care is to achieve acceptance for widespread clinical application in the hospital and community setting, it is important that its effect on short and long-term cardiovascular (CV), stroke and renal outcomes is studied and validated. The following summary reviews the literature on nurse-led hypertension clinics in relation to their effect on macrovascular and renal outcomes compared to primary care.

Search Strategy

A literature search was performed on the electronic databases OVID Medline®, PubMed, ScienceDirect, the Cochrane database, CINAHL, and other university library resources including E-journals for studies from peer-reviewed journals that looked at the comparison of nurse-led hypertension clinics to primary care

follow-up and associated macrovascular and renal outcomes. Search terms used included 'hypertension, blood pressure control, intervention, community, nurse-led care, collaborative team, primary care, cardiovascular risk, macrovascular, renal function, renal outcomes, microalbuminuria, macroalbuminuria, glomerular filtration rate, serum creatinine, cardiovascular outcomes, stroke, randomised controlled trials.'

Nurse-led model of care for blood pressure control, macrovascular and renal risk

While several studies have demonstrated an effective reduction in BP using a nurse-led model of care in comparison to conventional care,[159,160,173,177-182] there is a distinct lack of randomised controlled trials (RCT) demonstrating the comparative effect of these models on macrovascular and renal outcomes. There are no published studies evaluating short or long-term CV or stroke outcomes secondary to BP control through nurse-led hypertension care. Two studies,[160,180] one utilising a collaborative team approach (involving a nurse/community healthcare worker/physician),[180] have examined the effect of nurse-led clinics on respective BP and lipid control, and on the management of other CV risk factors, and have calculated the predicted CV risk following intervention. Another study, also utilising a nurse-led collaborative team approach has looked at the effect of BP control on left ventricular mass (LVM) and left atrial (LA) volume,[173] two cardiac parameters frequently affected by chronic, uncontrolled hypertension.[183] In regard to renal outcomes, the respective Denver[160] and Hill[173] studies are the only RCTs that have examined the effect of nurse-led clinics on BP control and renal outcomes. The other studies, discussed below, were prospective, interventional studies.[181,182]

Macrovascular risk

An important RCT conducted by Denver,[160] examining the effectiveness of a nurse-led hypertension clinic in patients with type 2 diabetes and hypertension looked at the effect of BP control on respective CV and stroke risk. Patients were randomised to either a nurse-led clinic or to conventional primary care.

Those in the nurse-led clinic were seen on a monthly basis for the first 3 months of the study, and then 6-weekly for 3 months. Antihypertensive medication changes were initiated by the nurse, in adherence to recommended hypertension treatment guidelines, if BP was above the target level (>140/80mmHg for patients without renal complications, >120/70mmHg for patients with renal complications). A treatment algorithm was not used. A study physician provided prescriptions for antihypertensive medication as required.

While well-matched at baseline, a lower systolic BP was seen in the nurse-led group (141.1[19.3]mmHg versus 151.0[21.9]mmHg, p=0.02) after 6 months, with target systolic BP achieved in 38% of the nurse-led group versus only 12% of the conventional care group (p=0.003). Diastolic BP was similar in both groups.

Reductions in respective 10-year coronary heart disease (CHD) (p=0.004) and stroke (p<0.001) risk scores were achieved in the intervention group. The median number of antihypertensive agents in the nurse-led group was three compared to two in the control group, which was unchanged from baseline (p=0.016).

The key determinants that led to greater improvement in BP control and resultant CV risk reduction in the nurse-led group were presumed to be secondary to the increased frequency of clinic visits and the nurse-initiated changes to antihypertensive medication regimens, with rigorous adherence to BP treatment guidelines, resulting in a greater likelihood and frequency of antihypertensive treatment adjustment.

Another RCT examined the effectiveness of a community-based multiple risk factor intervention, utilising a nurse-led collaborative team approach to reduce CHD risk in high-risk, underserved Black American families.[180] 364 high-risk siblings of Black probands <60 years of age hospitalised for a CHD event were

randomised to either a community-based care (CBC) group, or an 'enhanced' primary care (EPC) group.

One of the primary aims of the study was to eliminate some of the well-known barriers to care, including transportation and financial barriers. In the EPC group, those who required pharmacotherapy received charge service cards for free risk factor medications. Primary care providers were sent national guidelines material on recommended BP and lipid treatment, and were made aware of the charge service cards that their patients had been allocated. The above measures constituted the 'enhanced' care service for the EPC group.

Risk factor criterion for study entry included current smoking, LDL cholesterol ≥3.37mmol/l, and/or average systolic BP ≥140mmHg, or an average diastolic BP ≥90mmHg.

Subjects randomised to the CBC group attended nurse-led clinics. The clinic chosen for the CBC group was easily accessible by public transport for the study families, and many lived within walking distance to it. It was not necessary to make an appointment to see the nurse and community healthcare worker, who were available 9am-5pm Mondays to Fridays, and on Saturdays if requested.

BP monitoring was performed by the nurse along with a medication compliance review. Medication changes were made by the nurse in adherence to national guidelines on BP control and lipid management, and the patient's primary care provider was informed of any changes to medication. The primary care providers were requested to refrain from providing care for criterion risk factors and not to make adjustments to related pharmacotherapy. Also, each subject requiring pharmacotherapy was provided with a charge service card which enabled them to obtain their risk factor medications for free.

The community healthcare worker saw the subjects for dietary and exercise counseling and smoking cessation advice. The exercise programme included two free evening exercise sessions per week at the local YWCA, conducted by the

community healthcare worker. Respective mean (SD) baseline BP was 139(16)/89(10)mmHg in the CBC group and 137(16)/86(11)mmHg in the EPC group.

After 12 months follow-up, the CBC participants had an average of 7.4±8 CBC encounters over the study period and a third of these encounters were by telephone.

By the end of the study, systolic and diastolic BP were lower in the CBC group (mean(SD) systolic BP: CBC 130(14)mmHg vs EPC 134(17)mmHg (p=0.0001), mean(SD) diastolic BP: CBC 84(9)mmHg vs EPC 85(10)mmHg (p=0.0002)). The CBC group was twice as likely to achieve BP and LDL cholesterol target levels compared to the EPC group. A 16.2% decrease in smoking occurred among smokers in the CBC group compared to a 7% reduction in the EPC group. 48% in the CBC group received a charge service card, compared to 21% in the EPC group (p<0.0001). 74% of the CBC group used their card to fill prescriptions compared to 34% of the EPC group (p<0.0001). The Framingham risk score for total CHD in the CBC group had a decrement of 25.5% compared to only 3.3% in the EPC group (p<0.0001).

Another study involving a nurse-led collaborative team approach examined the effect of an educational-behavioural-pharmacologic intervention on BP control, progression of LV hypertrophy (LVH), and renal insufficiency in 309 patients with hypertension, from a low socioeconomic and underserved population group.[173] Patients randomised to the intervention group underwent regular clinic visits scheduled with the nurse, who made therapeutic decisions including medication dosage changes, in adherence with a protocol based on national hypertension treatment guidelines. A community healthcare worker visited the patient at home at least once a year during the study, providing referrals to social services, and assisting with housing issues. Follow-up was for 3 years. The intervention group achieved greater systolic and diastolic BP decrements than the control group (-7.5/-10.1 mmHg [intervention group] versus +3.4/-3.7 [control group],

between-group differences in systolic [*p*=0.001] and diastolic BP [*p*=0.005]), decreased progression of LVH, with lower LVM in the intervention group (274 grams (g)) versus the control group (311g) (*p*=0.004). Linear regression analysis showed a smaller increase in LVM in the CBC group compared to the EPC group (*p*=0.006).

Renal risk

The study by Denver[160] looked at the effect of good BP control on albuminuria levels. The majority of the patients (71%) in the study had increased urinary albumin excretion (UAE). No significant change was seen in the respective UAE or serum creatinine levels in the intervention group at the end of the study, despite the achievement of good BP control. The Hill study[173] found a trend towards a delay in progressive renal function decline, with a lower annual incidence rate of reaching a 50% increase in serum creatinine seen in the intervention group (5.2%) compared to the conventional group (8.0%) (*p*=0.08).

There are few RCTs in the literature focusing on renal outcomes in nurse-led hypertension clinics. Two studies (both prospective, interventional studies) reviewed the effect of nurse-led BP control on renal outcomes in patients with type 2 diabetes, hypertension and nephropathy, whereby treatment changes were implemented through the use of an antihypertensive treatment algorithm.[181,182] The studies were conducted at the same nurse-led clinic, at separate chronological periods. In the first study, 110 patients were seen in the nurse-led clinic on a monthly basis until BP targets were met (BP<130/80mmHg).[181] They were then discharged from the clinic, and were reviewed 9 months later. The total period of treatment was approximately 14 months, inclusive of the 9 month treatment review. The mean BP decreased from 140/85mmHg to 130/68mmHg on discharge from the clinic (*p*<0.001). BP control was sustained at the 9 months follow-up review (133/67mmHg), and the number of patients with microalbuminuria had decreased from 47% to 28%

(p=0.02), with a urinary albumin to creatinine ratio (ACR) decrease from 3.0 (1.3-7.9)mg/mmol to 1.8 (1.0-5.0)mg/mmol (p=0.01).

The second study followed the progress of 71 patients at the same nurse-led clinic, in adherence to an antihypertensive treatment algorithm.[182] At study entry, 72% of the patients had microalbuminuria and 28% had established diabetic nephropathy. Patients were seen on a monthly basis until BP targets were met. They were then discharged from the clinic, and seen 12 months later for review. The total treatment duration, including the 12 month treatment review, was 18-20 months. At the end of the study, 58% of the patients had achieved target BP compared to 25% at study entry (p=0.001). The mean urinary ACR decreased from 8.4 ± 5.3mg/mmol at baseline to 4.6 ± 4.2mg/mmol at the 12 month follow-up review (p=0.0003). Estimated glomerular filtration rate (GFR) decreased over the study period, from 82 ± 22µmol/l to 72 ± 22µmol/l (p<0.0001). A contributing factor to this was presumed to be an increase in the use of renin-angiotensin-aldosterone system (RAAS) blocking agents over the intervention period, leading to a reduction in GFR.

Conclusion

Nurse-led hypertension clinics appear to be more effective than conventional care in reducing BP. Evidence from these studies suggests a reduction in surrogate CV endpoints. Two of the above studies demonstrated an improvement in calculated CV risk, one implementing a collaborative team approach.[160,180] The other study,[173] which demonstrated a regression in LVH, provides further leverage for the potential benefits of this model, given that LVH is associated with an increased risk of CV disease in patients with hypertension,[184] and that the risk of future CV events is reduced when LVM is reduced by antihypertensive treatment.[185]

There is a distinct lack of studies looking at the effectiveness of nurse-led hypertension clinics on BP control and renal outcomes in patients with diabetes. Two of the studies discussed above[181,182] are both limited by the fact that

neither were RCTs. The only RCT to look at renal outcomes in patients with diabetes attending a nurse-led hypertension clinic was the Denver study.[160] No changes were seen in albuminuria levels by the end of the study. However, more than 80% of each group were taking antihypertensive agents that interrupted the RAAS at baseline, so it is possible that this may have influenced the lack of UAE difference between the groups by the end of the study.

There is much scope for further research to evaluate the effectiveness of a nurse-led model of care on CV, stroke and renal outcomes, and a cost-effective analysis is an important component to this, given the constraints on local and nationwide healthcare resources, and a need to find healthcare delivery models that are cost-saving. The importance of identifying, addressing and removing patient barriers to care is illustrated well in one of the studies.[180] The modification of transport barriers and financial barriers associated with clinic costs and prescription charges are likely to have contributed to the effectiveness of the community-based model of care in achieving BP targets and reducing CV risk.

2.3 24-hour ambulatory blood pressure monitoring in patients with diabetes and chronic kidney disease

Introduction

Ambulatory blood pressure monitoring (ABPM) has emerged as an important diagnostic and prognostic tool in hypertension and cardiovascular disease (CVD). Its usefulness has been established in both clinical practice and research. In comparison to office BP, ABPM has often been shown to be superior in predicting target organ damage and future CV outcomes in patients with essential hypertension, as well as those within the general population. The role of ABPM in patients with diabetes and chronic kidney disease (CKD) respectively is discussed in this chapter, including the comparison of ABPM to office BP measurement in predicting CV and renal outcomes.

Search Strategy

A literature search was performed on the electronic databases OVID Medline®, PubMed, ScienceDirect and other university library resources including E-journals for studies from peer-reviewed journals, on the use of 24-hour ABPM in essential hypertension, diabetes and CKD. Search terms used included 'randomised controlled trials, diabetic nephropathy, chronic kidney disease, end-stage renal disease, 24-hour ambulatory blood pressure monitoring, daytime, night-time, dipper, non-dipper, pulse pressure, microalbuminuria, macroalbuminuria, type 2 diabetes, prognosis, hypertension, cardiovascular outcomes'.

Advantages of Ambulatory Blood Pressure Monitoring

Good BP control is important to delay the progression of diabetic nephropathy, and ABPM is a useful tool to help identify and target BP abnormalities that are seen in greater prevalence in patients with diabetes and CKD. ABPM has a number of advantages over office BP and home self-monitored BP. A 24-hour record of the BP is obtained, and any "white coat" effect is removed. BP readings obtained over this period can provide information on circadian

rhythmic changes in BP, including BP during sleep. This is the major advantage of ABPM over home BP monitoring,[186] and has importance given the association of abnormal circadian rhythm with target organ damage and adverse CV and renal outcomes. It can also provide information on ambulatory pulse pressure (PP) and heart rate variability, which have respectively been shown to be important prognostic factors for future target organ damage, and CV and renal outcomes.[187-189]

Technical Aspects of Ambulatory Blood Pressure Monitoring

There are two techniques for measuring ambulatory BP. The most common method used involves intermittent BP measurement over a 24-hour period. The other method involves a continuous waveform analysis, providing beat-to-beat monitoring and producing waveform measurements similar to intra-arterial recordings.[190]

There are two main BP detection methods in ABPM. The auscultatory method detects the onset and disappearance of Korotkoff sounds by a microphone placed over an artery distal to a deflating compression cuff, while the oscillometric method, the more common method used, relies on detection of oscillations as they appear as the compression cuff deflates below systolic BP.[190]

Reference Values for Ambulatory Blood Pressure Monitoring

Reference values have historically been derived from population studies of normotensive subjects, and are based on the statistical distribution of BP values.[191-193] However, there is limited evidence that these statistically-derived reference values predict morbidity and mortality.[194] Reference values have also been derived from the findings of large prospective outcome studies, and are based on the optimal range of ambulatory BP values associated with the lowest CV risk.[189,195-200] Amalgamating the results of prospective outcome studies, the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) group has provided outcome-driven ambulatory BP thresholds.[194] BP values obtained by ABPM are several mmHg

lower than corresponding office BP values. A 24-hour ambulatory BP of 125/80mmHg corresponds to a clinic reading of 140/90mmHg.[201] The following reference values for daytime and night-time ambulatory BP in adults are recommended by the European Society of Hypertension (ESH) and the American Heart Association (AHA).[202,203] (Table 4). The 24-hour ambulatory BP reference values are recommended by the AHA.

Table 4: Recommended standards for normal ambulatory blood pressure levels.[202,203]

Average BP (mmHg)	Daytime	Night-time	24-hour
Optimal	<130/80	<115/65	<125/75
Normal	<135/85	<120/70	<130/80
Abnormal	>140/90	>125/75	>135/85

Unlike office BP, there are no reliable standard reference values for ambulatory BP in people with diabetes and CKD.

Circadian blood pressure abnormalities in diabetes and chronic kidney disease

A normal circadian BP pattern is characterised by a fall in nocturnal BP, occurring during the first few hours of sleep, followed by a surge in the early morning. The nocturnal decrease in BP has been termed "dipping". A meta-analysis of 23 studies, examining circadian BP patterns in the general population showed that the typical fall in night-time systolic BP was 13% and 17% in diastolic BP.[191] A nocturnal decrease of <10% for both diastolic and systolic BP is abnormal,[204] and is termed 'non-dipping'. Abnormal patterns of circadian BP, with loss of nocturnal dipping are more prevalent in subjects with diabetes and CKD respectively than in patients with essential hypertension only.[205-216] Cohen et al demonstrated a higher prevalence of elevated night-time BP in 28 normoalbuminuric patients with type 1 diabetes compared to 28 normotensive subjects without diabetes, who were matched for baseline office BP.[217] 78% of the diabetes group versus 39% of the other group had a loss of nocturnal

dipping in BP (p=0.007).[217]

Loss of nocturnal dipping in normoalbuminuric patients with type 1 diabetes has also been shown to increase the risk of developing microalbuminuria[80] and is associated with the presence of microalbuminuria in patients with type 1[209-211] and type 2 diabetes.[206-208] Subjects with type 1 diabetes and microalbuminuria have higher night-time BP than normoalbuminuric subjects with type 1 diabetes or normal age-matched controls.[209-211] Microalbuminuria may be present in 15% of patients with newly diagnosed type 2 diabetes, with a high proportion of these patients exhibiting hyperfiltration and only 21% having a normal circadian BP profile on ABPM.[218] In a study of 171 patients with hypertension and predominantly type 2 diabetes that looked at the relationship between elevated night-time BP and urinary albumin excretion (UAE), patients with a night-time diastolic BP $\geq$75mmHg had a four-fold increased risk of abnormal UAE compared to those with a night-time diastolic BP <75mmHg.[219]

There is evidence that abnormal ambulatory BP profiles increase in prevalence as renal dysfunction progresses. The loss of nocturnal dipping occurs more frequently as CKD progresses, from 15% in normal subjects to 75% of subjects reaching CKD stage 5.[220] Toth et al compared diurnal BP patterns of patients with type 1 diabetes and end-stage renal disease (ESRD) receiving renal replacement therapy (RRT) in the form of continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis (HD) to patients with diabetes and normoalbuminuria or microalbuminuria respectively.[221] Higher daytime and nocturnal BPs in addition to loss of nocturnal dipping were more prevalent in patients with ESRD compared with other groups.

A number of possible underlying mechanisms that lead to an alteration in circadian rhythm in patients with diabetes have been proposed. CV autonomic neuropathy, which can manifest as orthostatic hypotension and decreased heart rate variability on 24-hour monitoring, is found in patients with type 1 and type 2 diabetes at an increased prevalence.[222-224] One study evaluating the

association of CV autonomic neuropathy to microalbuminuria in 132 patients with type 2 diabetes found that UAE rates were highest in those with decreased heart rate variability.[225] Obstructive sleep apnoea, a common finding in obese patients with type 2 diabetes, and closely associated with hypertension, may contribute to the elevation of nocturnal BP.[226] Hypertension in CKD is accentuated by pathophysiologic changes including extracellular fluid retention, salt sensitivity, abnormal activation of the sympathetic nervous system, and release of various vasoactive factors that result in abnormal vasoconstriction,[227] and all of these factors are likely to contribute to circadian rhythm abnormalities.[227,228]

Ambulatory blood pressure monitoring and left ventricular hypertrophy

Ambulatory BP has been shown to correlate more closely with left ventricular hypertrophy (LVH) in hypertensive subjects, when compared to office BP.[229-231] A closer correlation of LV mass index (LVMI) with night-time systolic and diastolic BP than with daytime or office BP has been demonstrated, and LVMI is also increased in those with a non-dipping BP profile.[231] For patients with CKD, ABPM has proven to be more predictive of LVMI than office BP. In a study of 85 patients with mild to advanced CKD, nocturnal systolic BP was found to be the main determinant of LVH in the patients with advanced renal impairment.[232] In another study, the relationship between ABPM and LVH was evaluated in 29 paediatric patients with CKD. 21% were found to have LVH, and a higher 24-hour systolic BP was the only independent predictor for increased LVMI.[215] In ESRD, non-dipping occurs in the majority of haemodialysis patients, and occurs in greater prevalence in this group compared to patients receiving CAPD. While non-dipping has been associated with an increase in LVMI in haemodialysis patients,[233] one study reported that volume overload was the main independent determinant of LVH in haemodialysis patients as opposed to a non-dipping status.[234]

The role of ABPM in predicting LVH regression has also been demonstrated in a study of patients with hypertension and echocardiographic evidence of LVH who were examined to assess whether a reduction in LVM induced by long-term antihypertensive treatment was more accurately predicted by a decrease in office or 24-hour ambulatory BP.[235] Prior to the commencement of study treatment, LVMI correlated with systolic and diastolic 24-hour BP, but not with office BP. Regression of LVH was more strongly predicted by treatment-induced changes in average 24-hour systolic BP than office BP.

There is a paucity of published literature on the role of ABPM in predicting LV regression in subjects with diabetes and CKD respectively.

Ambulatory blood pressure monitoring and cardiovascular outcomes

The prognostic role of ABPM in determining CV morbidity and mortality has been assessed in a large number of studies, involving subjects from the general population and those with treated and untreated essential hypertension respectively.[189,195-199,236-241]

Ambulatory systolic BP has consistently been shown to be a stronger predictor of CV mortality risk compared to office systolic BP, with night-time BP, and in particular a non-dipping status shown to be the most potent predictor of CV outcome in some studies.[189,195-199] There is limited prospective data assessing the prognostic significance of ABPM in patients with diabetes and CKD. Several small retrospective and cross-sectional studies have been carried out.

Nakano et al evaluated the significance of circadian rhythm abnormalities as a predictive factor for fatal and nonfatal vascular events in 325 patients with type 2 diabetes who were followed up for an average duration of 4 years.[188] The presence of an abnormal circadian BP, older age and diabetic nephropathy were all associated with higher relative risks for vascular events. A similar association between loss of normal circadian BP variation and an increased mortality rate was found in a retrospective 4-year follow-up study assessing the relevance of circadian BP variation to future morbidity and mortality in 75 subjects with

either type 1 or type 2 diabetes.[238] The highest mortality rate was seen in subjects with renal impairment and a non-dipping status. In ESRD patients on haemodialysis, the non-dipping phenomenon and elevated nocturnal BP have respectively been shown to be potent predictors of CV morbidity and mortality.[187,242]

A wide 24-hour PP has been shown to be a significant predictive factor for CV events in a study of 2010 patients with essential hypertension.[187] Ambulatory PP was superior to office PP in predicting CV morbidity. Similar findings were seen in a prospective study of 228 subjects with type 2 diabetes, without prior history of CV events, where subjects with a wide PP were more likely to have a CV event within a 100-month follow-up period.[189] A wide 24-hour PP is also a potent predictor of CV events and mortality in ESRD patients on haemodialysis.[187,242]

Ambulatory blood pressure monitoring and renal outcomes

The value of using ABPM to predict the progression of diabetic nephropathy has been demonstrated in a number of studies. Knudsen et al evaluated the predictive value of non-dipping and PP abnormalities on progression of nephropathy in 112 patients with type 2 diabetes.[243] Patients were followed for an average of 9.5 years, and underwent respective baseline and follow-up ABPM and urinary albumin measurements. Impaired nocturnal dipping in diastolic BP and increased ambulatory PP were found to be strong independent risk factors for progression of nephropathy. This was also demonstrated in a retrospective study of 26 patients with diabetes in which non-dipping was associated with a more rapid decline in creatinine clearance of -7.9ml/min/year compared to the 'dipper' group, which had a rate of creatinine clearance decline of -2.9ml/min/year (p<0.05).[244]

Agarwal & Andersen looked at the role of ABPM compared to office BP in predicting ESRD and death in a cohort of 217 veterans with CKD who were followed for a mean duration of 3.5 years.[245] ABPM was found to be a stronger

predictor of ESRD and death than office BP. Non-dipping was associated with an increased risk of total mortality and composite endpoint, and elevated 24-hour systolic ambulatory BP increased the risk of ESRD. However, after adjustment for other risk factors for CKD progression including diabetes, age, and proteinuria, the value of ABPM as an independent predictor of renal and CV outcomes diminished. Subsequent to the above study, Minutolo et al looked at the prognostic role of daytime and night-time systolic BP versus office BP in 436 patients with CKD from a heterogeneous population.[246] Primary endpoints were time to renal death (ESRD or death), and time to fatal and nonfatal CV events. Median follow-up was 4.2 years. The mean glomerular filtration rate (GFR) was 42.9ml/min/1.7m^2. 36.5% had diabetes and 30.5% had CV disease. 155 patients reached the renal endpoint and 103 patients reached the CV endpoint. Patients with either higher daytime or night-time systolic BP had an increased risk of renal death and of reaching the CV endpoint. Office BP measurement was not predictive of the risk of renal or CV endpoints respectively. Non-dipping and reverse dipping were both associated with an increased risk of either end point.

Conclusion

Abnormal circadian BP profiles are demonstrated early in the spectrum of diabetic renal disease, and may precede the onset of microalbuminuria. Moreover, a greater rate of decline in renal function is predicted by the presence of an abnormal circadian BP pattern. Autonomic neuropathy may account for the abnormalities in circadian BP profiles in patients with diabetes, and pathophysiologic changes leading to fluid retention and abnormal vasoconstriction can occur in patients with CKD. There is evidence that ABPM correlates strongly with target organ damage, and has prognostic significance for future CV events and progressive decline in renal function. There are few large prospective studies examining the role of ABPM as a predictor of renal and CV events in groups with diabetes and CKD, irrespective of the cause of renal disease. The increased prevalence of hypertension and abnormal circadian rhythm patterns in patients with diabetes and CKD, and the prognostic

implications of elevated ambulatory BP and impaired circadian rhythm highlight the importance of the need for future prospective studies examining these groups. Ambulatory BP reference values specifically for patients with diabetes and CKD, based on the optimal range of BP values associated with the lowest CV risk would be an important step forward in the management of BP control in these groups. The optimisation of BP control is an important factor in slowing the progression to ESRD and reducing CV risk.[119,120] The role of ABPM in identifying the individual patient's degree of BP control over a 24-hour duration can be used as a guide in tailoring antihypertensive treatment to treat the individual patient, in an effort to decrease the risk of future target organ damage, renal function decline and CV morbidity and mortality.

2.4 Discussion of a model of care for blood pressure control based around nurse coordinators and visiting healthcare assistants of Māori or Pacific origin

Māori and Pacific people with diabetes experience poorer health outcomes than the general population with diabetes in New Zealand (NZ).[22,23,27,48,111,247] Ineffective healthcare delivery systems and factors resulting in clinical inertia (as previously discussed in chapter 2.1), and a lack of service provision appropriate and acceptable to Māori and Pacific communities have contributed to poor outcomes.[247] Māori and Pacific people experience socio-economic disadvantage in NZ, and personal barriers such as cost barriers, (inability to afford user co-payments for primary care appointment fees and prescription co-payments), transport barriers (precluding patients from attending clinic appointments, collecting prescriptions, and having laboratory tests done in a timely manner), language barriers, cultural and psycho-social barriers all play a major role in reducing access to healthcare in these groups.[247]

Findings from a retrospective audit conducted in 2002 by Nand and Collins through the Auckland City Hospital Renal Service [248] served as an important platform for the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study (discussed in chapters 3 to 5). The audit looked at factors contributing to the rate of progression of diabetic nephropathy to end-stage renal disease (ESRD), and reviewed a random sample of 50 patients with ESRD secondary to diabetic nephropathy, commencing renal replacement therapy (RRT) (dialysis or transplantation) between 1997-2002. Referral patterns to the Renal Service, patient ethnicity, pre-dialysis blood pressure (BP) control, the pre-dialysis use of angiotensin converting enzyme (ACE) inhibitors, the rate of glomerular filtration rate (GFR) loss (calculated by the Cockcroft-Gault equation), and the duration of time from the first clinic visit at the Renal Service to the commencement of RRT were reviewed.

60% of patients were male. 50% of patients were Māori or Pacific, 22% were Indian, 24% were Caucasian and 4% others. 94% of patients had hypertension,

36% had peripheral vascular disease, 26% had a history of ischaemic heart disease, and 16% had evidence of left ventricular (LV) impairment.

72% of patients were on ACE inhibitor therapy at any time during follow-up, and 20% had ACE inhibitor therapy discontinued. Reasons for discontinuation of ACE inhibitor therapy included intolerance of the medication due to cough, unresolving hyperkalaemia, and suspicion of renal artery stenosis. 8% of patients had an unclear reason for discontinuation of therapy.

44% of patients were referred to the Renal Service by a general practitioner (GP), 32% by a hospital medical team and 24% by a diabetes clinic. 68% of patients had a GFR <30ml/min/1.73m^2 at the time of referral. The average length of follow-up from first clinic visit to commencement of dialysis was 5 months (range 3-96 months), and the mean number of clinic visits was 5 (range 3-16). 44% of patients received dialysis within 12 months of referral.

Patients were divided into groups according to their rate of GFR decline:

1. Group 1 < 1ml/min/month (*n*=27)
2. Group 2 1-2ml/min/month (*n*=16)
3. Group 3 >2ml/min/month (*n*=7)

Māori and Pacific patients comprised the majority of group 2 (56%) and group 3 (71%), and comprised 37% of group 1 (*p*=0.34). BP control (BP <145/85mmHg) was attained in 44% of group 1 compared to only 6% of group 2 and 14% of group 3 (*p*=0.08). ACE inhibitor use was seen in 77% of group 1 compared to 42% of group 2 and 57% of group 3 (*p*=0.52). The rate of GFR decline was significantly lower in the patients with BP <145/85mmHg compared to those with BP >145/85mmHg (median 0.74ml/min/month versus 1.14ml/min/month, *p*=0.008)

The findings in this audit illustrated the impact of poor BP control on the rate of progression of diabetic nephropathy to ESRD. Māori and Pacific patients were disproportionately represented in the groups with higher rates of poor BP

control, and had a more rapid decline of GFR to ESRD. These findings provided further evidence that the standard model of care for BP control used in the community and in the hospital clinic setting is suboptimal for Māori and Pacific patients with CKD secondary to diabetic nephropathy and hypertension.

Chapter 2.1 and 2.2 have described the evidence showing that nurse-led hypertension clinics can be more effective than routine primary care in reducing blood pressure (BP) and achieving BP targets, and can also lead to improved renal and cardiovascular (CV) endpoints. A collaborative approach with community-based multidisciplinary teams and community health workers has contributed to the effectiveness of these clinics. Regular and frequent patient follow-up, conducting clinics in the community and workplace, authorisation of nurses to adjust antihypertensive regimens with physician supervision, and adherence to stepwise hypertension treatment algorithms were identified as important contributing factors to the effectiveness of this model of healthcare delivery.

The objective of the study outlined in this thesis was to evaluate a model of care that delivered home-based management of hypertension to Māori and Pacific patients with type 2 diabetes and established diabetic nephropathy. This model was designed to encompass a number of factors associated with increased effectiveness of BP control in the community, and in addition to this, aiming to address the well known barriers that contribute to Māori and Pacific people having poorer access to healthcare services than the general population, through the utilisation of culturally appropriate healthcare assistants (HCA), support workers who would work under the supervision of a registered health practitioner (a study research nurse).

The following factors were considered vital components in the framework of the proposed model of care:

1. A nurse-led, integrated model of care involving frequent (monthly) follow-up of patients by a culturally-appropriate HCA at home or in the workplace for BP monitoring and adjustment of antihypertensive medication if BP targets are not met, saving the patient the cost of a primary care visit for BP monitoring and management
2. Frequent (monthly) review by an HCA of the patient's medication compliance, medication side effects and significant clinical events occurring over the previous month
3. The use of and adherence to an evidence-based antihypertensive medication protocol
4. HCAs having either iwi (tribe) affiliation or being of Pacific origin, having a close connection with, and an understanding of their own culture and their ethnic community
5. Pacific HCAs to be fluent in their own indigenous language
6. HCAs to bridge cultural gaps between healthcare professionals and patients
7. HCAs to take on a patient advocate role
8. HCAs to provide emotional and social support to the patients
9. HCAs to provide transport for patients coming to research clinic visits, to the local pharmacy for collection of prescriptions, and to the community laboratory for blood and urine tests
10. Provision of subsidised prescriptions for antihypertensive medications to the patients
11. A research nurse to supervise the HCAs and to educate the patients in diabetes, hypertension and kidney disease

Chapter 3 – Methods

DElay Future End-stage Nephropathy due to Diabetes (DEFEND) Study

3.1 Introduction

Ka pu te ruha, ka hao te rangitahi

As the old net withers, another is re-made[1]

The DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study was a novel, integrated model of care which used a collaborative team approach of physician-nurse-healthcare assistant (HCA), involving monthly community visits by Māori and Pacific HCAs to deliver home-based management of hypertension in Māori and Pacific patients with type 2 diabetes and established diabetic nephropathy. The DEFEND study incorporated several factors into the model of care, known to be effective in attaining BP control in the community. Māori and Pacific HCAs were utilised in the study because of their potential to improve access to healthcare for Māori and Pacific patients with diabetes, by acting as cultural mediators, bridging the cultural gaps through their understanding of cultural values particular to their own ethnicity, and offering social and emotional support and advocacy to the patients. They would also have a practical role in removing barriers to healthcare by conducting home-based visits and providing transportation to clinic appointments, to the local pharmacy for medication prescriptions and to the laboratory for blood and urine tests.

3.2 Aim and outline of the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study. Discussion of the inclusion/exclusion criteria, and the recruitment process, including screening, initial information visits and the randomisation process.

Introduction

The aim of the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study, a randomised controlled trial (RCT) was to determine whether a novel model of care involving monthly community visits by a nurse-led, culturally appropriate Māori or Pacific healthcare assistant (HCA) is more effective than conventional care in improving blood pressure (BP) control, and as a consequence would limit kidney and cardiac disease progression in Māori and Pacific patients with diabetic kidney disease and hypertension.

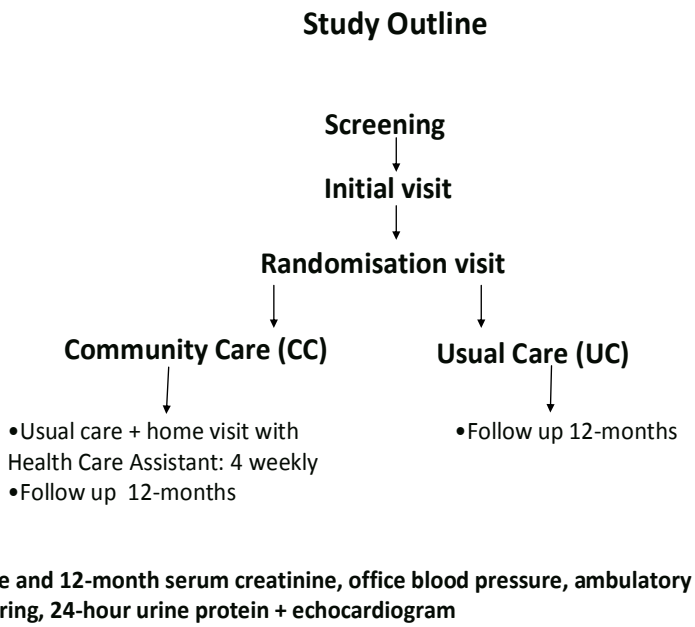


Figure 1: Outline of the DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study

Patients were screened and recruited through the hospital diabetes and renal clinics and primary care practices in two areas of Auckland, which provide comprehensive public health care for a population of about 900,000. The study was approved by the local ethics committee and received approval by the respective Māori and Pacific Island Health Services in the community and

hospital. Patients provided written, informed consent, using an interpreter when required.

Inclusion criteria were Māori and Pacific patients with type 2 diabetes, aged 40–75 years, with diabetic nephropathy (≥0.5g proteinuria/24-hour and serum creatinine 130–300µmol/l) and BP >130/80mmHg. Exclusion criteria included insulin dependence within 12 months of diagnosis of diabetes, evidence of non-diabetic renal disease and severe chronic illness including malignancy, heart failure, respiratory failure, psychiatric disorder and cognitive impairment.

The primary end point of the DEFEND study was a change in office systolic and diastolic BP. Secondary end points included a change in 24-hour urinary protein excretion, HbA_{1c}, total cholesterol and any change in cardiac parameters of left ventricular (LV) mass/body surface area (BSA), left atrial (LA) volume/BSA, and in E/E', the ratio of early transmitral inflow velocity (E) to medial mitral annular early diastolic velocity (E prime [E']), a measure of LV filling pressure.

Recruitment

The DEFEND study was originally intended to recruit several hundred participants. However, during recruitment, it was determined that significantly fewer patients would meet the inclusion criteria and thus be eligible for randomisation. To address the recruitment difficulties encountered, the principal investigators elected to change the serum creatinine inclusion criteria range to 100-300µmol/l (from 130-300µmol/l), or a GFR ≤60/ml/min/1.73m^2. 2,413 Māori and Pacific patients with type 2 diabetes were screened through the Central Auckland and North Shore diabetes and renal outpatient clinic registers. 1824 patients had a serum creatinine and/or 24-hour urinary protein levels below the threshold for inclusion in the study, while 264 patients had serum creatinine levels >300µmol/l. 255 patients had other significant medical problems to preclude them from entry into the study. 5 patients who met the inclusion criteria declined involvement in the study. Patients who met the inclusion criteria in the initial screening process were invited to attend a

DEFEND study information and registration visit, where they underwent formal screening to determine their eligibility into the study.

After inspection of unblinded BP data from the first 30 patients, the principal investigators elected to end recruitment at the end of the calendar year and to continue with a 12-month follow-up period. This resulted in 65 patients being available for randomisation.

UC=usual care CC=community care

Figure 2: Screening process in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

Randomisation

Patients were randomised to either the control (usual care [UC]) group or the intervention (community care [CC]) group by a computerised random-number generator, operated by the Auckland University Clinical Trials Research Unit (CTRU), Auckland, New Zealand. Electronic case record forms pertaining to each study participant were completed by DEFEND staff and submitted through a secure web server operated by the CTRU. Participants were then electronically registered directly into the CTRU central study database and underwent computer-generated randomisation into the study via this secure study website. CTRU staff managing the above database were not directly involved with any of the DEFEND study participants. Enrolment of the study participants was implemented by the study research fellow and research nurse. The preparation of a random sequence and of an allocation system was generated by the CTRU. Neither the trial participants nor those administering the interventions and measuring the outcomes were blinded to group assignment.

65 Māori and Pacific patients meeting the inclusion criteria were randomised into the UC (*n*=32) or CC (*n*=33) groups. Patients from each group underwent baseline and 12-month visits. The comparative echocardiographic study included 32 UC patients and 31 CC patients. The analysis was by "intention-to-treat."

Recruitment started on 1 November 2004. The first patient was randomised into the study on 10 November 2004, the last patient was randomised on 13 February 2006. Patients were followed up for 12 months.

3.3 Discussion of the training of the healthcare assistants in the DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study

Ko koe ki tēnā

Ko ahau ki tēnei

Kīwai o te kete

You hold that handle

And I'll lift this handle

And together we can carry the kete[1]

Healthcare assistant (HCA) candidates for the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study were required to complete a 12 week HCA certification course at an accredited New Zealand (NZ) technical institute. The 12-week course provided participants with basic healthcare training, to enable them to deliver a specific healthcare service within a limited scope. The course covered the following topics:

- The role of a caregiver
- Code of Rights
- Basic communication
- Basic activities of daily living provided to older people
- Manual handling training and biomechanics
- Infection control and hand washing
- Understanding health and safety
- Basic first aid
- The ageing process and quality of life
- Dementia

- Diet and nutrition
- Teamwork

The first nine weeks of the course were conducted at the technical institute, followed by three weeks in a clinical placement, working alongside an experienced HCA. All candidates were required to have a current full NZ driver's license. Candidates were chosen due to their affiliations with either Māori or Pacific communities. Pacific candidates were considered for recruitment if they were fluent in the language spoken by their own ethnic group.

The HCAs were recruited through advertisements placed in the Auckland District Health Board careers website, and positions were advertised at the two Auckland technical institutes which held the 12-week HCA certification courses.

Two HCAs, one of Māori ethnicity and Ngapuhi iwi (tribe) affiliation, the other of Tongan ethnicity and fluent in the Tongan language were recruited through the two respective technical institutes. The study investigators had anticipated the recruitment a Samoan HCA, given that Samoan people are the make up the largest proportion of Pacific people in NZ. However, recruitment of a Samoan HCA did not eventuate due to lack of funding and adequate HCA to patient ratios following employment of the other two HCAs.

On recruitment to the DEFEND study, the HCAs underwent an intensive educational training programme to prepare them for their role in the DEFEND study. The principal trainer of the HCAs was the DEFEND study research nurse specialist who had previous extensive clinical experience in renal medicine in NZ and in the United Kingdom. The following topics were covered within the training programme:

- Basic education on the clinical aspects of diabetes and chronic kidney disease (CKD) secondary to diabetic nephropathy

- Basic education on dietary modification in diabetes and CKD, including discussion on the benefits of low-fat, low-salt, and in some cases, low-potassium diets
- Education on the benefits of exercise
- Education around the methodology of the DEFEND study, and the role of the HCA in the study
- Basic education on the Treaty of Waitangi, and its significance to the health of Māori and New Zealanders as a whole
- Basic education on hypertension, antihypertensive agents, common medication side-effects
- Education on smoking cessation
- Basic computer skills
- Filing skills
- Familiarisation with the University of Auckland Department of Medicine (where their work base was situated), Auckland City Hospital, and Greenlane Clinical Centre, Auckland

Both HCAs attended respective diabetes and renal clinics within Auckland District Health Board as part of their training, to gain first-hand experience of the outpatient setting for patients with diabetes and renal disease. The clinics attended by the HCAs were respectively conducted by a diabetes physician, a renal physician, a diabetes nurse specialist, a renal nurse specialist, a diabetes dietitian, and a renal dietitian. The HCAs also spent time in the Auckland District Health Board haemodialysis and peritoneal dialysis units for experience with patients with end-stage renal disease (ESRD) receiving renal replacement therapy (RRT).

The ability to accurately monitor and record blood pressure (BP) in patients was a fundamental component of the HCA's role in the DEFEND study, and both HCAs underwent intensive training from the research nurse specialist on the practical use of both manual and automated office BP sphygmomanometers,

and on the use of the 24-hour ambulatory BP monitoring (ABPM) machines. The HCAs received instruction on how to measure office and 24-hour ambulatory BP in all of the DEFEND study patients at baseline and at the 12-month follow-up visit, and conduct monthly visits to the home or workplace of the patients in the community care (CC) arm of the study. The HCAs were also taught to conduct a questionnaire with the patients at each visit, asking about medication compliance, medication side effects and whether any changes had been made to the medication regimen, and whether any significant clinical events had occurred within the previous month (see Appendix A). The HCAs were also instructed on how to report the information gathered at the visit back to the study nurse and doctor and how to input the data into a computer.

During their training, the importance of the HCA's role as a cultural mediator was emphasised, to bridge the cultural gaps and language barriers that exist between the health service and Māori and Pacific communities. The importance of their role as a patient advocate, offering social and emotional support was also stressed.

3.4 Discussion of the process of monthly follow-up of patients randomised into the intensive community care group of the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

A detailed education package (see Appendix B) was developed for the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study and given to all patients. This focused on diabetes and its complications, the significance of maintaining good blood pressure (BP) control, the importance of compliance with medication use, exercise, cessation of smoking, and dietary modification, including avoidance of excessive salt intake. At baseline, all patients participated in an individual education session conducted by the research nurse. The community care (CC) group patients were visited monthly by a healthcare assistant (HCA). Seated BP was measured. Compliance with antihypertensive medication use was checked through a questionnaire (see Appendix A). Each CC patient reported their compliance as 'good' (taking medication most of the time), 'average' (regularly missing some medications), or 'poor' (hardly ever taking medications). BP results, possible medication side-effects, compliance issues and any significant clinical events occurring over the previous month were reported back to the study doctor and nurse. If BP was above target (>130/80mmHg), antihypertensive medications were changed by the study doctor in accordance with a stepwise protocol which included an angiotensin converting enzyme (ACE) inhibitor, a thiazide diuretic, a calcium channel blocker, a beta-blocker and an alpha-blocker if needed (Table 5). Medication adherence was promoted by feedback on the compliance questionnaire and positive encouragement at the monthly visits.

Patients in the CC group were offered transport if required to their local pharmacy to collect prescribed medications, to their local laboratory for blood and urine tests, and to the follow-up study clinic appointments. These patients continued to also receive routine care from their primary health-care physician and hospital outpatient clinic follow-up where required. Communication

occurred regularly between the DEFEND trial group and the patient's usual doctors.

The patients in the usual care (UC) group, on the other hand, only received routine family doctor and renal/diabetes hospital outpatient clinic care. No attempt was made to alter management of their BP by the DEFEND investigators, and these patients were seen by the study investigators at baseline and 12 months only.

3.5 Description of the antihypertensive medication protocol utilised in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

A stepwise antihypertensive medication protocol was implemented in the community care (CC) arm of the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study. For CC patients who were taking no blood pressure (BP) medications at the first monthly visit and whose BP was >130/80mmHg, the first step of the protocol was applied. If the patient was already taking antihypertensive medications and BP was >130/80mmHg, either a new antihypertensive agent was commenced or the dose of an existing antihypertensive agent was maximised by adhering to the protocol below (Table 5), to achieve a BP ≤130/80mmHg.

Table 5: DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study antihypertensive medication protocol for community care patients

Visit 1	If BP >130/80mmHg start Cilazapril 2.5 mg daily
Visit 2	If BP >130/80mmHg increase Cilazapril to 5 mg daily
Visit 3	If BP >130/80mmHg change to Cilazapril 5 mg/Hydrochlorothiazide 12.5 mg one daily (or add Bendrofluazide 2.5 mg daily)
Visit 4	If BP >130/80mmHg add Felodipine 2.5 mg daily
Visit 5	If BP >130/80mmHg increase to Felodipine 5 mg daily
Visit 6	If BP >130/80mmHg increase to Felodipine 10 mg daily
Visit 7	If BP >130/80mmHg commence Metoprolol 47.5 mg daily in patients who have no contraindications for this drug (asthma, hypoglycaemia-unawareness, severe peripheral vascular disease)
Visit 8	If BP >130/80mmHg increase Metoprolol to 95 mg daily
	(Visits carried out 4-weekly to the CC patients)

The stepwise protocol used in the DEFEND study had a target BP of ≤130/80mmHg. This protocol was based on the target BP recommended by international and national guidelines for the management of hypertension in patients with diabetes. The guidelines included the Seventh Report of the Joint

National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7),[141] the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI™) guidelines,[66] the American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2011[140] and the New Zealand Guidelines Group (NZGG) guidelines on the management of type 2 diabetes.[249]

While angiotensin receptor blockers (ARB) were recommended as first-line agents in the above guidelines, they were not included in this protocol due to NZ prescribing restrictions of this medication. Where the patient was already on antihypertensive medications, these were rationalised to once daily medications using the agents listed, or they continued to take existing alternative agents if assessed as appropriate and administered once daily. If a patient had not reached BP targets by visit 8 (table 5), then the research fellow would decide whether to increase the beta blocker dose further, or consider commencing an alpha blocker (Doxazosin).

3.6 Outline of baseline and follow-up investigations and statistical analysis undertaken in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

At the baseline visit in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study, a detailed medical history was obtained and a clinical examination was performed on each patient. Information obtained included the duration of diabetes, history of diabetic micro- and macrovascular complications, presence of other cardiovascular (CV) risk factors, co-morbidities, and current medications. Investigations conducted at baseline and at 12 months included seated office blood pressure (BP), 24-hour ambulatory blood pressure monitoring (ABPM), electrocardiography, 2-dimensional (2D) and Doppler echocardiography, serum biochemistry for creatinine, electrolytes, plasma glucose, HbA_{1c}, lipids and 24-hour urinary protein collection.

The seated office BP was measured in both arms using an Omron T9P automated BP device. Three measurements were taken at 1-minute intervals. The second and third measurements were averaged to give the mean systolic and diastolic BP. Right-sided office BP was the default BP used for data analysis. In cases where the left-sided average systolic BP recordings were significantly higher than the right (*n*=1 in the usual care (UC) group, *n*=3 in community care (CC) group), left-sided BP recordings were taken.

24-hour ABPM was conducted using a Del Mar Reynolds P6 Pressurometer 24-hour ABPM oscillometric device. The device was British Hypertension Society (BHS) certified and was chosen following a comparative assessment of cost-effectiveness (purchase and maintenance costs) with other ABPM models. The P6 Pressurometer had a BP measurement range of 60-250mmHg systolic and 30-195mmHg diastolic. It was powered by two disposable alkaline AA batteries.

The ABPM devices were calibrated to a mercury sphygmomanometer on a monthly basis. The device was programmed to obtain BP readings at 30-minute intervals during the daytime (0600h-2200h) and 1-hour intervals during the nighttime (2200h-0600h). Data from each device was downloaded using Del

Mar Reynolds software to give a comprehensive record of BP readings over the 24-hour period.

The DEFEND study research nurse received training on the use of the ABPM device from a representative of the medical supplies company that provided the devices. The research nurse subsequently trained the healthcare assistants (HCA) on the practical use of the devices. The DEFEND study patients received instruction on the monitoring procedure and were asked to keep a diary in which to record daily activity, posture, symptoms (such as dizziness), and times of sleep and medication administration. They were also instructed to keep their arm immobile when a BP measurement was occurring. Patients were provided with the contact details of the research nurse and HCA should any problems arise while the 24-hour ABPM was taking place.

A full clinical echocardiogram (Philips HDI 5000/iE33, Bothell, Seattle, WA) was performed at baseline and 12 months.[250] Left ventricular (LV) geometry (volume and wall thickness) and left atrial (LA) volume were determined and indexed to body surface area (BSA).[250] LV diastolic function was assessed using mitral valve inflow Doppler with the sample volume between the leaflet tips and tissue Doppler with a 5-mm sample volume on the medial aspect of the mitral valve annulus. The signals were optimised and recorded at 100 mm/second sweep speed. Images were acquired in digital format, and measurements were made at the end of the expiratory phase of normal respiration.

All echocardiograms were analysed by one experienced observer (blinded to treatment allocation) using an off-line workstation (Digiview,® Digisonics, Houston, TX). Each variable was measured in triplicate, and the average of the three measurements was used. LV filling pressure was assessed using E/E', the ratio of the peak early mitral inflow velocity (E) to medial mitral annular early diastolic velocity (E').

At the 12-month visit, a record was compiled of clinically significant events that had occurred over the study period. These included death, non-fatal myocardial infarction, new onset of angina, cerebrovascular accident, heart failure, new onset of symptoms of peripheral vascular disease, amputation, a vascular procedure (e.g. peripheral angiography), requirement for dialysis, and hospitalisation. Medication lists were reviewed. All patients underwent a further clinical examination.

Statistical Analysis

With two groups of 33 and 32 participants, respectively, the study had at least 80% power at the 5% significance level to detect a large (Cohen) treatment effect [69% of 1 standard deviation (SD)]. Data were analysed using a mixed model approach to repeated measures. Main effects of treatment allocation and time and their interaction were included in the model. Significant main or interaction effects were further explored using the method of Tukey. A *p*-value <0.05 was considered significant. All tests were two-tailed. Normality was assessed using the Shapiro–Wilk's statistic in SAS (version 9.1 SAS Institute, Inc.), as is appropriate for a smaller sample size.

Chapter 4 – Results

DElay Future End-stage Nephropathy due to Diabetes (DEFEND) Study

Respective baseline and one year follow-up results of the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study from October 2004 to February 2006

Baseline characteristics

The ethnic groups represented in the study included patients of Māori, Tongan, Samoan, Cook Island Māori, Niuean and Tuvaluan ethnicity. Both groups were well-matched in baseline characteristics (Table 6). The majority of the patients were in stage 3 chronic kidney disease (CKD), and a smaller number were in stage 4 CKD. The mean 24-hour urine protein excretion exceeded 3 grams (g) (range 0.5–23.2g/day), and the mean body mass index (BMI) exceeded 35kg/m^2.

32 UC patients and 31 CC patients underwent baseline echocardiography. Echocardiographic parameters including left ventricular (LV) mass/body surface area (BSA), left atrial (LA) volume/BSA, and E/E' were well matched between the groups (Table 6). Fifty-four percent of the patients had LV hypertrophy (LVH) at baseline.[263] None of the patients had normal LV diastolic function (E/E' and LA volume/BSA elevated). There was no difference between the groups in the number of prescribed antihypertensive medications at baseline (p=0.28) (Table 6).

Table 6: Baseline clinical data in 32 usual care (UC) and 33 community care (CC) patients with chronic kidney disease secondary to type 2 diabetes, randomised in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

	UC (*n* = 32)	CC (*n* = 33)	*p*-value
Age (years)	60 (7.1)	63 (6.6)	0.083
Gender M/F (*n*)	17/15	18/15	0.99
BMI (kg/m^2)	35.3 (5.8)	35.8 (6.9)	0.75
Duration of diabetes (years)	12 (6)	12 (8)	0.99
Insulin treated (*n*)	20	19	0.80
Duration of insulin use (years)	5.4 (5.2)	5.1 (4.6)	0.81
Smoker (ex or current) (%)	44	48	0.81
Diabetic retinopathy (%)	78	83	0.76
Peripheral neuropathy (%)	84	91	0.48
Ischaemic heart disease (%)	19	15	0.75
Cerebrovascular disease (%)	13	9	0.71
Peripheral vascular disease (%)	19	18	0.75
Number of antihypertensive agents	1.9 (0.9)	2.2 (1.3)	0.28
Office systolic BP (mmHg)	161 (20)	161 (20)	0.99
Office diastolic BP (mmHg)	85 (12)	88 (9)	0.26
Serum creatinine (µmol/l)	164 (52)	184 (69)	0.19
GFR (ml/min/1.73 m^2)	39 (14)	36 (15)	0.41
24-hour urinary protein (g/day) median (±IQ range)	1.60 (0.90, 4.00)	3.30 (1.45, 5.25)	0.12
HbA_{1c} (%)	8.5 (1.9)	8.3 (1.6)	0.64
Total cholesterol (mmol/l)	4.7 (1.2)	5.0 (1.8)	0.43
LVM/BSA (g/m^2) (normal <95 ♀ ≤115 ♂)[a]	146.3 (25.0)	135.0 (33.3)	0.13
LA volume/BSA (ml/m^2) (normal <29)	33.8 (8.8)	37.5 (11.0)	0.14
E/E' (normal <8)	13.6 (5.6)	13.1 (4.3)	0.69

Data are mean (± SD). [a]Baseline echocardiography conducted in 32 UC and 31 CC patients. Baseline LVM/BSA (UC n=25, CC=29), baseline LA volume/BSA (UC n=30, CC n=29), baseline E/E' (UC n=28, CC n=29)

The duration of follow-up for both groups was 12 months. One patient from the community care (CC) group required dialysis. Two patients from the CC group died during the study period, one of metastatic liver cancer (not clinically

apparent at recruitment) and the other of cardiac arrest likely secondary to ischaemic heart disease. Four usual care (UC) patients were lost to follow-up during the study. One patient from each group underwent coronary bypass grafting, and one from each group had a transient ischaemic attack. No significant differences were seen between the groups in cardiovascular (CV) outcomes.

12 month follow-up results

At 12 months, the CC patients were prescribed a significantly greater mean number of antihypertensive medications ($p<0.01$) (Table 7). This group achieved a significantly lower office systolic BP at 12 months compared to the UC group ($p=0.04$) (Figure 3 and Table 7). No significant difference in office diastolic BP was seen between the groups at 12 months (Figure 3 and Table 7). The CC group also achieved a significantly lower 24-hour urinary protein excretion at 12 months ($p=0.04$) (Figure 4 and Table 7). No significant differences were seen between the groups at 12 months for changes in serum creatinine, HbA_{1c} or total cholesterol (Table 7). We examined plots of the change in systolic BP and urinary protein from baseline to 12 months (Figure 5). While for each variable there were some patients who did show a marked change, these patients were not consistent across all variables. Those patients showing the most changes were not necessarily the same, and the correlation (Spearman) between the change in systolic BP from baseline to 12 months and change in urinary protein to 12 months was poor ($r=-0.15$, $p=0.26$).

Table 7: Comparative changes at baseline and 12 months in office blood pressure, renal function, HbA1c, total cholesterol and echocardiographic parameters in 32 usual care (UC) vs 33 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

	UC		CC	
	Baseline (*n* = 32)	**12 months** (*n* = 28)	**Baseline** (*n* = 33)	**12 months** (*n* = 30)
SBP (mmHg)**	161 (20)	149 (23)*	161 (20)	140 (19)*
DBP (mmHg)	85 (12)	77 (12)	88 (9)	78 (11)
eGFR (ml/min/1.73 m^2)	39 (14)	41 (18)	36 (15)	33 (17)
24-hour urinary protein (g/day)median (±IQ range)**	1.60 (0.90, 4.00)	2.20 (0.50, 5.10)*	3.30 (1.45, 5.25)	1.95 (0.50, 3.80)*
HbA_{1c} (%)	8.5 (1.9)	7.9 (1.7)	8.3 (1.6)	8.0 (1.9)
Total cholesterol (mmol/l)	4.7 (1.2)	4.5 (1.3)	5.0 (1.8)	4.4 (2.0)
Antihypertensives (n)	1.9 (0.9)	2.3 (1.0)	2.2 (1.3)	3.4 (1.1)*
LVM/BSA (g/m^2)**	146.3 (25.0)	163 (33.3)*	135 (33.3)	131.5 (25.4)*
LA volume/BSA (ml/m^2)**	33.8 (8.8)	36.7 (10.8)*	37.5 (11)	35.3 (9.5)*
E/E'	13.6 (5.6)	14.8 (5.1)	13.1 (4.3)	12.4 (2.5)

Data are mean (± SD). *p<0.05 (12 months vs baseline). **p<0.05 CC vs UC at 12 months. Baseline LVM/BSA (UC n=25, CC=29), baseline LA volume/BSA (UC n=30, CC n=29), baseline E/E' (UC n=28, CC n=29)

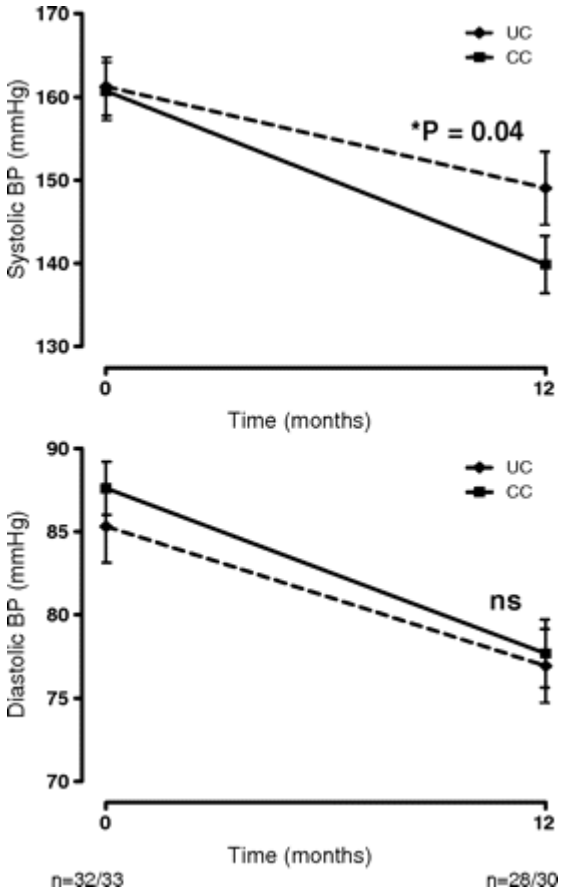


Figure 3: Comparative changes in mean (± standard error of the mean) systolic and diastolic BP from baseline to 12 months in 32 usual care (UC) patients vs 33 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

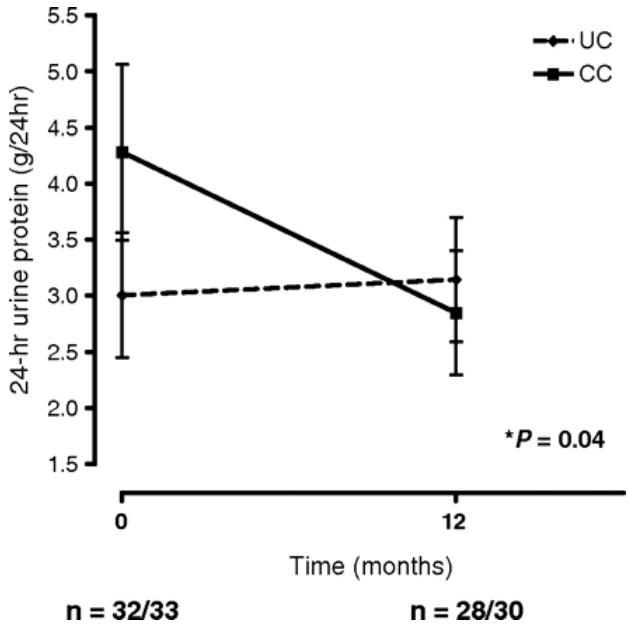


Figure 4: Comparative changes in mean (± standard error of the mean) 24-hour urinary protein from baseline to 12 months between 32 usual care (UC) patients vs 33 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

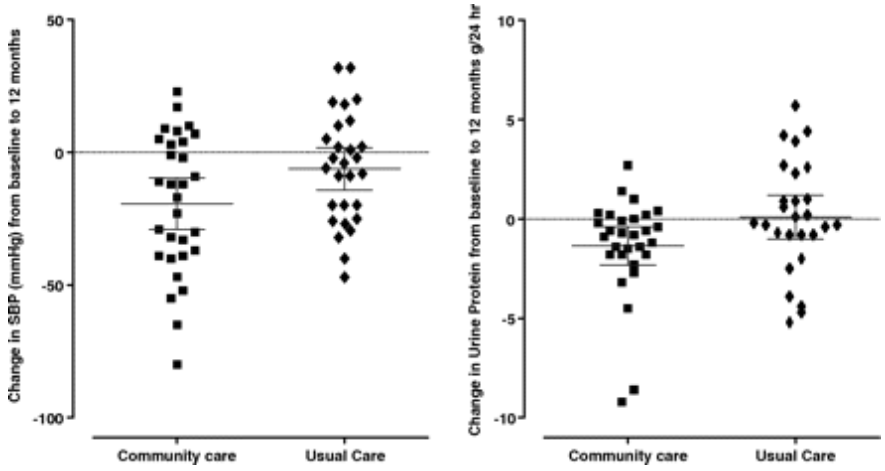


Figure 5: Individual responses from baseline to 12 months in systolic BP and 24-hour urinary protein excretion in 32 usual care (UC) patients and 33 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study. The correlation between change in systolic blood pressure and 24-hour protein excretion was poor (*r*=−0.15, *p*=0.26).

Four patients from the UC group were lost to follow-up. Assuming a worst-case scenario, we imputed the mean change to 12 months in the CC group and applied that to those subjects with missing data in the UC group. As anticipated from this overly conservative approach, the *p*-values for all end points increased (*p*=0.11 for change in 24-hour urinary protein, *p*=0.051 for systolic BP and *p*=0.24 for diastolic BP). In the best-case scenario where the average change in the UC group was imputed to those UC patients lost to follow-up, the probabilities were *p*=0.033 for change in 24-hour urinary protein, *p*=0.02 for systolic BP and *p*=0.11 for diastolic BP. A third middle-ground scenario is possible where the parameters for the 4 UC patients lost to follow-up did not change over the course of the study (the carry forward last visit approach). This scenario yields *p*=0.036 for urinary protein, *p*=0.028 for systolic BP and *p*=0.16 for diastolic BP.

28 UC patients and 29 CC patients underwent follow-up echocardiography at 12 months. Significant echocardiographic differences were seen between the groups at 12 months (Table 7). LV mass (LVM)/BSA increased in the UC group, but did not change in the CC group (*p*=0.0055). (Figure 6, Figure 7). LA volume/BSA increased in the UC group, while an improvement was seen in the

CC group (*p*=0.016) (Figure 8, Figure 9). There was a trend toward reduction in E/E' in this group, although this did not reach statistical significance (*p*=0.13) (Figure 10, Figure 11).

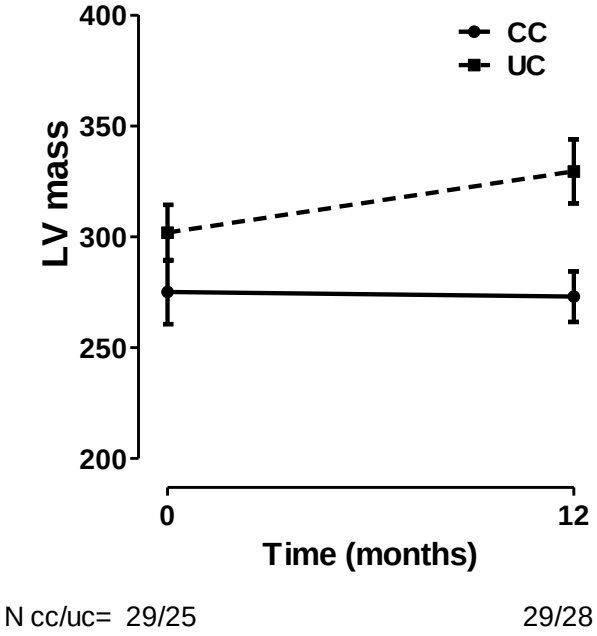


Figure 6: Comparative changes in mean (± standard error of the mean) left ventricular mass from baseline to 12 months in 25 usual care (UC) patients and 29 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study (*p*<0.05)

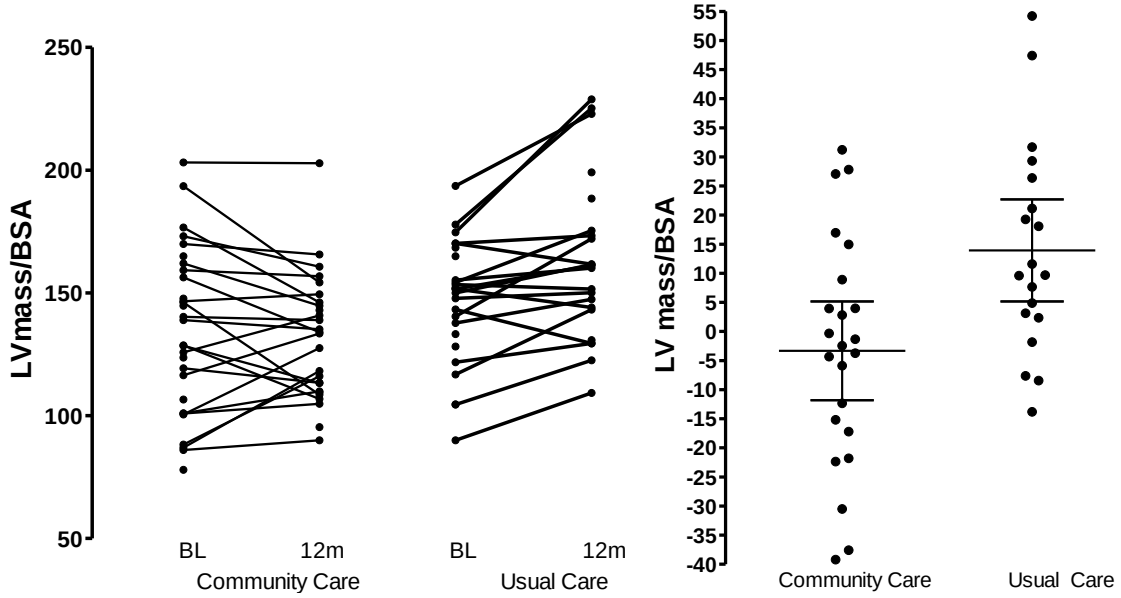


Figure 7: Individual responses from baseline to 12 months in left ventricular mass/body surface area in 25 usual care (UC) patients and 29 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

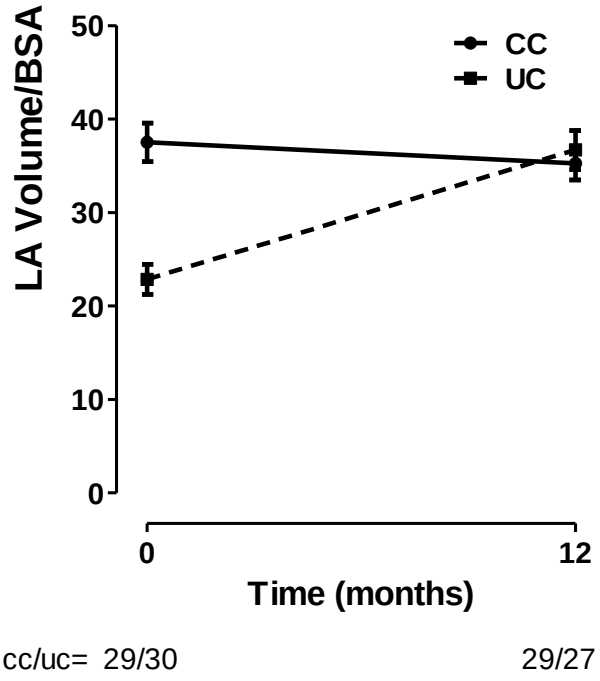


Figure 8: Comparative changes in mean (± standard error of the mean) left atrial volume/body surface area from baseline to 12 months in 30 usual care (UC) patients and 29 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study (p<0.05)

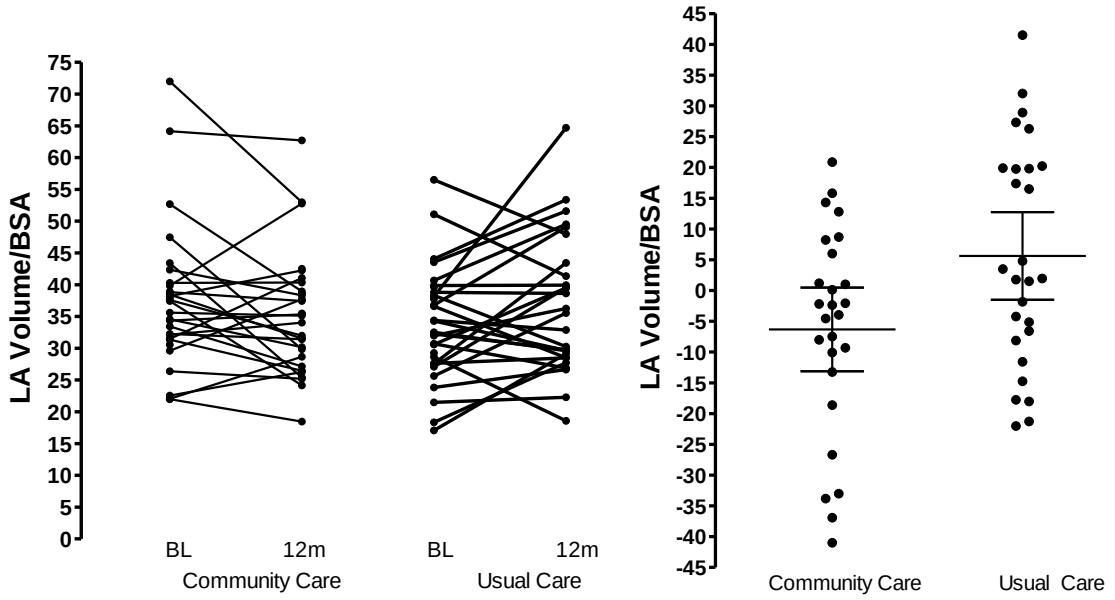


Figure 9: Individual responses from baseline to 12 months in left atrial volume/body surface area in 30 usual care (UC) patients and 29 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

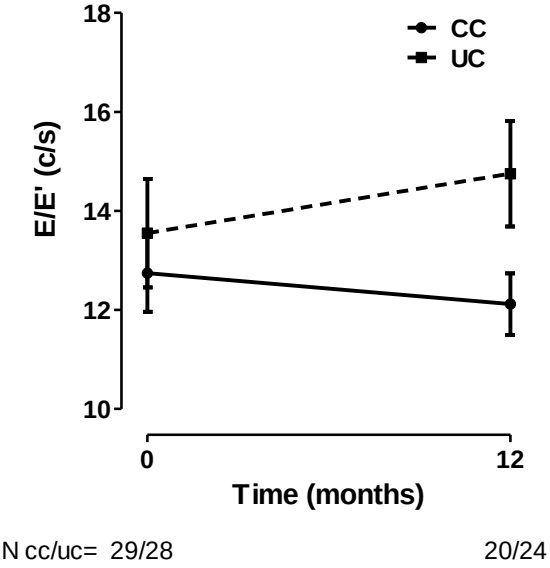


Figure 10: Comparative changes in mean (± standard error of the mean) E/E' from baseline to 12 months in 28 usual care (UC) patients and 29 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study (*p*=0.13)

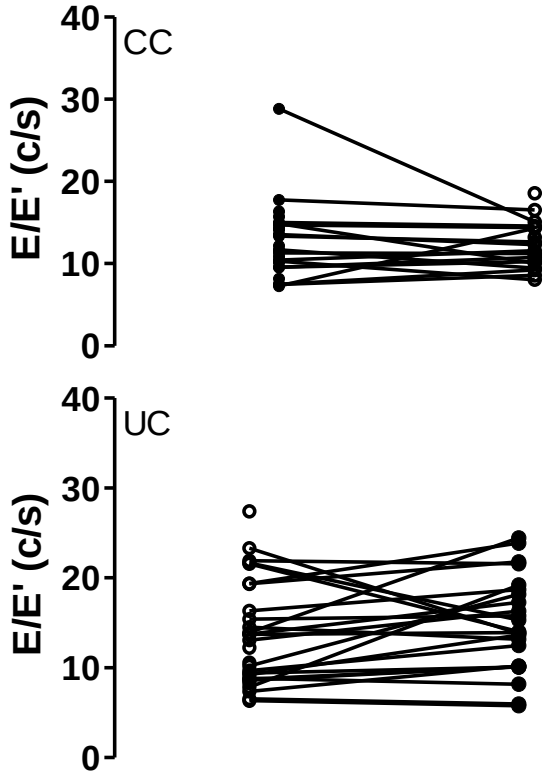


Figure 11: Individual responses from baseline to 12 months in E/E' in 28 usual care (UC) patients and 29 community care (CC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

The baseline and 12-month office systolic BP and diastolic BP results in the DEFEND study were evaluated to see whether there was any correlation between change in BP and compliance to antihypertensive medications. Patients assessed as having good compliance were compared to those with poor compliance (see Appendix A). The patients with good compliance at 12 months achieved reductions in mean BP whether or not they had been managed in the CC group (Table 8). CC patients achieved a reduction in mean BP even if they were assessed to have poor medication compliance. In contrast, UC patients with poor medication compliance had no improvement in BP over the 12 month study duration.

Table 8: Correlation between change in office blood pressure from baseline to 12 months and antihypertensive medication compliance in 30 community care (CC) patients and 28 usual care (UC) patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study

Compliance type (treatment arm)	Mean change in SBP (mmHg) (95%CI)		Mean change in DBP (mmHg) (95%CI)		Patient number (*n*)
Good (CC)	-17	(-27 to -8)	-7.4	(-12 to -2)	24
Good (UC)	-13	(-21 to -6)	-7.2	(-13 to -2)	20
Poor (CC)	-27	(-68 to -14)	-15.0	(-28 to -2)	6
Poor (UC)	+12	(-4 to +28)*	+1	(-7 to +8)**	8

A significant difference was seen in the mean change of office systolic BP (p=0.031) and diastolic BP (p=0.015) in the UC group with poor compliance compared to the CC groups with good and poor compliance and the UC group with good compliance.

As discussed in further detail in chapter 5, major technical difficulties with the ABPM devices occurred at baseline, resulting in incomplete recordings obtained over the 24-hour period in the majority of the patients. The inclusion of the 24-hour ABPM results in the study was consequently abandoned due to a failure to achieve adequate baseline data.

In summary, after 12 months of 4-weekly visits by the HCAs, the CC group had achieved a significant reduction in systolic BP compared to the UC group. A significant reduction in urinary protein level was also seen in the CC group as well as a respective improvement in LV mass and LA volume, while a progressive increase in LA volume was seen in the UC group.

Chapter 5 – Discussion

DElay Future End-stage Nephropathy due to Diabetes (DEFEND) Study

Chronic kidney disease (CKD) secondary to diabetic nephropathy in Māori and Pacific people with diabetes in New Zealand (NZ) is associated with poor outcomes and high health and economic costs.

Cardiovascular disease (CVD) is prevalent in the CKD population, and patients with CKD are more likely to die from CVD than from renal failure. Progressive renal function decline correlates in a graded manner with a greater risk of death, CV events and hospitalisation, and the risk of adverse events rises sharply once the estimated glomerular filtration rate (eGFR) is <45ml/min/1.73m^2.[96]

Cardiac end-organ damage is associated with an increased risk of both CV and renal disease.[251] Left ventricular hypertrophy (LVH), an important marker of preclinical CVD, is an independent predictor of myocardial infarction, stroke and CV death in patients with hypertension.[184,252,253] Progressive LV diastolic dysfunction with preserved systolic function is also an independent predictor of CV morbidity and mortality,[254] and all-cause mortality,[255] and is associated with a faster decline in renal function.[256] Both hypertension and diabetes are independent predictors of diastolic dysfunction,[257] and greater diastolic impairment occurs when these conditions are co-existent.[257]

As previously discussed in this thesis, there is a multitude of evidence to show that good blood pressure (BP) control, particularly by the use of renin-angiotensin-aldosterone system (RAAS) blocking agents, can delay progression of diabetic nephropathy to end-stage renal disease (ESRD)[94,119-123,125,126] and improve long-term CV outcomes.[94,121,123,124] There is also ample evidence illustrating that good BP control can prevent or improve cardiac end-organ damage such as LVH and diastolic dysfunction, and reduce the risk of future CV morbidity and mortality.[185,258,259] However, good BP control is difficult to achieve in the community and there is a need to develop models of healthcare delivery

that result in effective implementation of evidence-based treatment for hypertension.

The patients in the DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study were high-risk patients with complex medical problems, including advanced renal and cardiac end-organ disease. All of the patients had proteinuria. More than half of the patients had echocardiographic evidence of LVH, and none of the patients had normal diastolic function. They had longstanding, poorly controlled hypertension, which was refractory to the standard model of care for BP control used widely in the community, due to a failure of that model to effectively target and treat this population of patients, and furthermore, the presence of multiple barriers to care precluded the opportunity for effective chronic disease management to be implemented. While there is evidence from a previous study that ethnicity may be a factor in the rate of progression of renal disease in these groups,[110] hypertension was a major and important contributor to their progressive cardiac and renal disease.

The DEFEND model of care involved 'task shifting' (tasks previously performed by the physician became tasks undertaken by the nurse/healthcare assistant (HCA) team), resulting in an increase in direct patient encounters with the HCA, which were overseen by the research nurse, and less direct patient encounters occurred with the physician.

The DEFEND study demonstrated, in a randomised controlled design, that an integrated model of care using culturally-appropriate community healthcare workers can effectively lower BP in Māori and Pacific patients with chronic diabetic kidney disease and cardiac end-organ disease, and that a reduction in BP can translate into a reduction in the progression of end-organ damage.

By 12 months, the community care (CC) group had achieved lower office systolic BP compared to the usual care (UC) group (p=0.04) (Figure 3 and Table 7). Despite the presence of advanced renal end-organ damage in these patients, within 12 months we were able to show a reduction in proteinuria in the

intervention group, likely secondary to the reduction in systolic BP. Proteinuria is a surrogate marker for kidney damage, and a reduction in both proteinuria and BP is expected to result in a delay in CKD progression.

No significant differences were seen between the groups at 12 months for changes in serum creatinine, however the study was not powered to show that kind of benefit, and the duration of the study was not likely to have been long enough to detect a difference.

With regard to echocardiographic changes seen, the DEFEND study intervention prevented a progressive increase in LV mass in the CC group that was conversely observed in the control group, and led to an improvement in LV diastolic function, demonstrated by the improvement in left atrial (LA) volume in the CC group. There was no difference in CV events between the two groups at 12 months, although the beneficial effects on LV structure and diastolic function seen would suggest that such effects are plausible within a larger study, with a longer duration of follow-up.

While we cannot exclude the possibility of a type 1 error (at a probability of 5%) in either the LV function or proteinuria results seen in the CC group, by applying the Bradford-Hill criteria,[260] (defined as a group of minimal conditions necessary to provide adequate evidence of a causal relationship between an incidence and a consequence), the strength of the effect for both LV function and proteinuria are of the order of magnitude that one would expect from BP lowering. Therefore, the respective LV function and proteinuria results are consistent with each other, and biologically plausible. No changes were noted in HbA_{1c} or total cholesterol at 12 months (Table 7), but these parameters were not directly targeted by the intervention. At 12 months, the CC patients were prescribed a greater mean number of antihypertensive medications than the UC group (p<0.01) (Table 7).

The respective improvements seen in systolic BP, cardiac and renal parameters in the CC group in comparison to the higher systolic BP and progression of

cardiac and renal disease noted in the UC group are important findings in this study.

There are a number of factors within this model of care that are likely to have contributed to its effectiveness in achieving target outcomes. Several barriers to care that often confront this population of patients were addressed, and measures were implemented to facilitate intensification of antihypertensive therapy, shown in previous studies to reduce clinical inertia and increase the likelihood of reaching BP targets.[159,160,173,180-182]

Frequent and regular follow-up visits for BP monitoring, in conjunction with the utilisation of an antihypertensive medication protocol, previously shown to be effective in reducing therapeutic inertia and reaching target BP goals,[160,173,181,182] were incorporated into the DEFEND study. The CC patients underwent regular 4-weekly follow-up visits by the HCAs for the 12 month duration of the DEFEND study, followed by regular review of the 4-weekly BP results for each CC patient by the study doctor and nurse, with modification to each patient's antihypertensive medication regimen when indicated, in adherence to the stepwise treatment protocol (table 5).

An effective recall system to ensure regular and frequent follow-up visits for hypertension care is an important contributing factor to treatment intensification, and can lead to a reduction in BP, and a decrease in future CV risk.[174] To ensure follow-up visits occurred, an informal recall system was utilised in the DEFEND study, and this involved the HCA arranging a subsequent follow-up visit at each 4-weekly home visit. The HCAs also contacted the patients 2-3 days prior to the next visit to confirm the follow-up visit. This process was overseen by the research nurse.

Outreach services have been shown to reduce clinical inertia and improve BP control.[159] The regular home-based visits conducted by the HCAs to the CC patients for BP management addressed two important barriers to care (financial and transport) that the patient may have encountered by attending a usual

primary care or secondary care clinic visit. Transport was provided by the HCAs to the community laboratory for blood and urine tests, and to the community pharmacies to collect patients' prescribed medications, which were subsidised.

In addition to addressing the above barriers to care, other important benefits were gained by utilising the HCAs in the DEFEND study. They helped bridge cultural gaps between the patients and the healthcare providers by providing a culturally-appropriate face to clinical care, and their innate knowledge and understanding of their respective cultures facilitated their ability to build trusting relationships with the patients, particularly those of their own ethnicity and culture. Both HCAs were able to detect certain cultural nuances and interpret body language and other non-verbal cues particular to their culture that others on the research team were unaware of. Familiarity of the HCAs with acceptable and appropriate behaviours specific to their own cultures, and enlightenment of the research team to these cultural nuances decreased the risk for miscommunication between patients and healthcare providers. The HCAs also took on patient advocacy roles, and offered social and emotional support to patients and their families. At each 4-weekly visit, the HCAs encouraged and motivated the CC patients to take their medications as prescribed. They gained the trust of the patients under their care, and this is likely to have contributed to improving medication compliance in the CC patients. Both good medication compliance and frequent community follow-up by the HCAs were associated with an improvement in BP control. The language barrier present for the Tongan patients who did not speak English was removed by the Tongan HCA, who spoke fluent Tongan, and this saved the cost of an interpreter, who would have otherwise been provided by the district health board interpreting service.

We did, however, identify important limiting factors in using HCAs in the capacity of a frontline healthcare worker. Minimal healthcare qualifications, and a lack of clinical skills and expertise resulted in the HCAs having a limited scope of practice. The research nurse in charge of training and supervising the

HCAs reported that while they had become increasingly proficient in their roles throughout the study period, particularly in their ability to measure and record the CC patient's BP during home visits, the HCAs were reliant on the nurse for clinical input. They were not authorised to make any changes to a patient's medication regimen. Also, if a clinical problem or query arose during a home visit, the HCAs were unable to provide the patients with any medical expertise, including provision of medical advice, and they were dependent on the research nurse to intervene. If a problem occurred, the research nurse would be contacted by the HCA, and she would often visit the patient herself, and decide whether they required a medical review. On most occasions, the research nurse was able to resolve the problem herself. However, if a medical opinion was warranted, she would contact the research doctor for clinical advice, or arrange for the patient to see their general practitioner. The above clinical pathway was time-consuming and cumbersome, and highlighted an important limiting factor for HCAs to practise as independent frontline healthcare workers for BP management.

Occasionally, inadequate clinical information was obtained by the HCA at a home visit. This included inadequate BP recordings, or a lack of documentation about medication side effects or significant clinical events. If this occurred, the research nurse would either arrange for the HCA to conduct a repeat home visit to gather the missing information, or conduct a repeat visit herself.

The Tongan HCA encountered a number of issues during the course of the study. The HCA was married to a Tongan church minister, and had difficulty interviewing some of the DEFEND study patients because of their senior status within the church community. For example, one of her assigned patients was a Samoan minister, and the HCA felt unease in asking him medication compliance questions, so the research nurse was required to intervene, and interview the patient herself to find out this information. A number of the Tongan patients knew the Tongan HCA through a community association, and a couple of the patients were reluctant to share information about their health with this HCA,

concerned that she may inform other people in their mutual social and church circles.

Limitations

Limitations were identified during the course of the DEFEND study. Difficulties arose in the recruitment of subjects for the DEFEND study, and this led to a change in study endpoints, and changes to the inclusion criterion serum creatinine. Difficulties occurred in the 24-hour ambulatory blood pressure monitoring (ABPM) sub-study. Inadequate echocardiographic results were obtained in some of the patients. A cost-effective analysis of the DEFEND study was not conducted. These limitations are summarised below.

a) Recruitment of patients in the DEFEND study

The most important limitation in the DEFEND study occurred due to difficulties recruiting subjects into the study. The study was originally designed to have a doubling of the baseline serum creatinine as its primary endpoint, and was powered (90%) to detect a 10% absolute change (two-tailed) in the proportion of the CC patients versus the UC patients who reached this endpoint. These calculations were based on observations noted by Lewis et al[125] in a study which compared the renoprotective effects of irbesartan to amlodipine in 1,715 patients with type 2 diabetes, diabetic nephropathy and hypertension. After 3 years of follow-up, the serum creatinine concentration in 30% of the control group had doubled. A total sample size of 850 (two groups of 425 each) was estimated to be required to detect a difference between the groups in a doubling of the serum creatinine, with an allowance for 20% loss to follow-up.

The DEFEND study originally intended to recruit several hundred participants. However, during recruitment, it was determined that significantly fewer patients would meet the inclusion criteria and be eligible for randomisation. Recruitment was formally reviewed by the DEFEND study management committee after all potential patients in the study cohort had been screened. It was decided that given the futility of achieving the required sample size, the

original design of the study would be abandoned. Recruitment was then terminated, but this was made without recourse to analysis of the data. An amendment to the study protocol was made, and a change in office systolic and diastolic BP became the new primary endpoint. Pre-specified secondary endpoints (a change in 24-hour urinary protein excretion, HbA_{1c}, total cholesterol, a change in 24-hour ambulatory BP parameters, and a change in cardiac parameters of left ventricular (LV) mass/body surface area (BSA), left atrial (LA) volume/BSA, and E/E') were analysed with the acceptance that only large treatment effects could be detected (see section on statistical power in chapter 3). Since these were essentially secondary data analyses, no adjustment for multiple tests was employed.

b) Inclusion criteria - serum creatinine

When the recruitment difficulties in the DEFEND study became apparent, the DEFEND study principal investigators elected to change the inclusion criteria serum creatinine range from 130-300µmol/l to 100-300µmol/l. Following this change in the range of serum creatinine for inclusion into the DEFEND study, recruitment difficulties continued. Patients who fitted inclusion criteria on initial screening were invited to a pre-randomisation visit, where they underwent formal assessment of inclusion and exclusion criteria, to determine their eligibility into the study. All of the 65 patients randomised into the DEFEND study fitted the inclusion criteria. Patients underwent a further set of investigations at randomisation (reported in Table 6 as the baseline investigations). Three of the patients randomised into the DEFEND study, whose serum creatinines fitted the inclusion criteria at the pre-randomisation visit had subsequent baseline serum creatinines which were out of the inclusion criteria range. Regression to the mean occurred, which can be expected when a cut-off is applied for an inclusion criterion. On the 'intention to treat' principle, these patients were included in the study on the basis of their formal screening serum creatinine, obtained at the pre-randomisation visit. As

demonstrated in Table 6, there was no significant difference in mean serum creatinine at baseline between the two groups.

c) 24-hour ambulatory blood pressure monitoring sub-study

We aimed to conduct a 24-hour ABPM sub-study as part of the DEFEND study to compare ambulatory BP in the CC and UC groups at baseline and at 12 months. A number of contributing factors led to inadequate baseline ambulatory BP results being obtained. Technical difficulties with the ABPM devices occurred at baseline, resulting in incomplete recordings obtained over the 24-hour period in the majority of the patients. 5 of the 65 randomised patients did not undergo baseline 24-hour ABPM. Only 18 out of 60 patients (30%) achieved >7 baseline night-time BP recordings in adherence to recommended guidelines.[261] Battery failure was a major factor. Of the 60 patients who underwent baseline ABPM, battery failure occurred in 29 patients (48%). Eveready® AA alkaline batteries were used at baseline, and these were subsequently replaced by Energiser® AA alkaline batteries when the problems associated with the Eveready® batteries became apparent. 53 patients underwent follow-up 24-hour ABPM at 12 months. No battery failure occurred at 12 months with the Energiser® batteries. It is unclear why battery failure occurred with the Eveready® brand of batteries, but it was assumed to be related to the quality of the product.

Obesity and hypertension in the DEFEND patients are likely to have contributed to the technical problems that resulted in inadequate data obtained. The majority of the DEFEND study patients were obese, and although large BP cuffs were used, it was difficult to achieve a perfect cuff fit due to the shape of the cuff and the shape of the patient's arm. This appears to have resulted in the machine performing frequent cuff inflations in an attempt to detect BP. The DEFEND study patients were hypertensive, and in many cases, patients had markedly elevated BP. The combination of frequent cuff inflation and high pressures being attained by the cuff resulted in considerable discomfort to the patients, and this led to many patients prematurely removing the cuff from their

arm. Despite education and instruction given to the patients on the use of the ABPM devices, patient unfamiliarity with the device, and the inability to identify when problems arose contributed to the majority of the patients having inadequate baseline 24-hour ABPM results. The patients who experienced problems with the ABPM device did not attempt to call the DEFEND study staff after hours, despite being given instruction to do so, and it usually wasn't until the staff visited the patient to retrieve the machine that they were informed that problems had occurred. One particular problem that occurred with some of the night readings was that the night-time key on the ABPM device was not always activated, leading to a minimal number of night-time readings. Given the lack of adequate ABPM data obtained at baseline, further analysis of the sub-study was abandoned.

d) Cost-effective analysis of the DEFEND study

A cost-effective analysis was not performed in the DEFEND study due to the relatively high numbers of staff compared to patients, following the low recruitment numbers, resulting in low patient to HCA-nurse-doctor ratios. In a real clinic setting, it is likely that patient to staff ratios would be several-fold higher than those in the DEFEND study, and therefore the results of a cost-effective analysis of the DEFEND study would poorly reflect costs or potential cost savings if the same model of care was applied to a real clinic situation.

e) Echocardiographic parameters

Figures 6-11 illustrate that the echocardiographic parameter results are reported in a variable number of patients. The lower numbers of patients are a reflection of inadequate echocardiograhic data being obtained in some of the patients. 2-dimensional (2D) imaging can be affected by body habitus, particularly if the patient is obese, and can result in poor images. Cardiac rate or rhythm disturbances, such as tachycardia, ectopy or atrial fibrillation can also affect the quality of measurements obtained, in particular, Doppler echocardiographic parameters. Some or all of these factors may have

contributed to the inadequate echocardiographic data obtained in some of the patients.

Conclusion

Without effective methods of healthcare delivery for BP control, Māori and Pacific patients with type 2 diabetes, similar to those participating in the DEFEND study, are likely to continue to experience progressive renal and cardiac end-organ damage with high rates of CV morbidity and mortality. We demonstrated in the DEFEND study that several factors within this model of care contributed to lowering BP, and reducing target organ damage in high risk Māori and Pacific patients with advanced diabetic nephropathy and cardiac disease. Our study findings showed that regular and frequent patient follow-up for BP monitoring, in conjunction with strict adherence to a step-wise antihypertensive medication algorithm increased treatment intensification. The implementation of an outreach service, where patients were seen in their homes or in the workplace, and the provision of transport to enable patients to collect prescribed medications increased access to healthcare for patients who were restricted financially, or by lack of transport. The utilisation of culturally-appropriate frontline healthcare workers in a model of healthcare delivery for BP control in Māori and Pacific patients with diabetes had not been evaluated in previous studies. Benefits were gained by using the HCAs to deliver care to the CC patients, including their role in addressing the financial, transport, language and cultural barriers to care, and by building trusting relationships with the patients, which facilitated their ability to promote and encourage medication compliance. However, the HCA's limited scope of clinical practice and lack of clinical independence resulted in a reliance on the research nurse for clinical input and continual supervision over the study period. Their limited qualifications, and lack of clinical expertise restricted their ability to function independently as frontline healthcare providers in an outreach hypertension clinic, and components of their role are likely better conducted by experienced nurses.

The above factors identified within the DEFEND model of care that collectively strengthened its effectiveness are not routinely utilised in the hospital or primary care setting. Previous studies have demonstrated that the nurse-led model of care for BP control can easily be implemented into a routine clinical outpatient setting and deliver effective healthcare.[181,182] Given the simple community-based approach of the DEFEND study intervention, components of this model of care could successfully be applied to a primary care or hospital outpatient service for hypertension care, to enhance treatment intensification of BP and increase the likelihood of BP goals being reached. Primary healthcare services are the main providers of hypertension care in NZ, therefore primary care is likely to be the most appropriate setting in which to apply such a model of care. Components of this model could effectively be used in patients with diabetes and hypertension over a wide spectrum of severity of cardiac and renal disease secondary to diabetes and hypertension, as this study demonstrated its effectiveness in patients with advanced cardiac and renal disease.

The findings in the DEFEND study set an important platform for future research. The DEFEND study follow-up period was only 12 months duration, and there is scope for a longer study using a similar model of care for BP control, to evaluate long-term renal and CV outcomes in these high risk patients. It is likely that a greater number of patients could be recruited if the inclusion criteria were not limited to patients with moderate to advanced renal disease. It would be important to incorporate the components of the DEFEND study model of care which were likely to be effective in reaching target outcomes. While there are benefits in utilising the HCAs to address the cultural, language, financial and transport barriers to healthcare, we would recommend increased nursing input at the frontline of outreach care, to enable the patients to receive greater clinical expertise beyond what the HCAs are able to provide.

We demonstrated a number of important benefits in using culturally-appropriate healthcare workers to bridge cultural gaps between healthcare services and communities. Our findings suggest that there are benefits to be

gained by expanding the Māori and Pacific health workforce in NZ, and by improving and enhancing cultural understanding and competence within the general health workforce. There is, however, a need for further constructive evaluation of the effectiveness of these approaches.

Chapter 6 – Conclusion

DElay Future End-stage Nephropathy due to Diabetes (DEFEND) Study

The literature reviews, the cross-sectional evaluation, and the discussions presented throughout this thesis illustrate the higher rates of type 2 diabetes and obesity, and the poor health outcomes in Māori and Pacific people with diabetes in New Zealand (NZ), compared to NZ Europeans and the general NZ population. These groups also have a higher prevalence of diabetic nephropathy, occurring at a younger age compared to NZ Europeans and the general population. Diabetic nephropathy occurs in Māori and Pacific people after a shorter duration of diabetes, and its progression is more rapid in these groups, who also appear to have an increased genetic susceptibility to kidney disease, with studies demonstrating a familial predisposition to chronic kidney disease (CKD). Māori and Pacific people with CKD secondary to diabetic nephropathy have a greater number of hospital admissions from renal causes. They are also significantly more likely to develop end-stage renal disease (ESRD) secondary to diabetic nephropathy, and death rates are high in Māori with CKD and ESRD. Both groups are much less likely to be on the renal transplant waiting list, or indeed receive a transplant. Many Māori and Pacific patients with near-ESRD or ESRD have multiple co-morbidities precluding them from being accepted onto transplant waiting lists. Māori ESRD patients have significantly greater co-morbidity than other ESRD patients, with coronary artery disease, stroke, peripheral vascular disease, chronic lung disease and smoking rates higher in this group. Co-morbid prevalence rates in Pacific ESRD patients follow the rates in Māori, and are well ahead of NZ European and the general population rates respectively. Chapter 1.4 describes the multitude of evidence demonstrating the effectiveness of good BP control on diabetic nephropathy, particularly with the use of agents such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), which interrupt the renin angiotensin aldosterone system (RAAS). These agents can

effectively decrease proteinuria levels and slow the progression of diabetic nephropathy to ESRD. They are also effective in reducing cardiovascular (CV) outcomes. Despite the overwhelming evidence available on the effectiveness of antihypertensive agents to lower blood pressure (BP) and reduce future risk of respective CV and renal outcomes, effective management of BP is not widely achieved in everyday practice, and the majority of the hypertensive population have inadequately controlled BP. Several approaches to BP control in the community have been studied, and many, including nurse-led care, pharmacist-led care and the community-based use of a collaborative team approach have been shown to be effective as long as certain principles are applied within the model. The cardinal factors necessary to effectively control BP in the community include a robust system of patient registration and recall in conjunction with regular and frequent patient follow-up visits for BP monitoring and review of medications, compliance and side effects. Further effectiveness is gained by the use of and adherence to stepwise algorithms to change antihypertensive medications if target BP is not met, in accordance to recommended BP guidelines.

The effectiveness of nurse-led hypertension clinics is thought to be due to a higher utilisation of antihypertensive medications through more frequent follow-up, longer appointment times and greater adherence by nurses to medication protocols and guideline recommendations. However, the effectiveness of this model of care is dependent on the authorisation of nurses to initiate changes to a patient's medication regimen, either by physician or nurse adjustment of doses of existing medications and prescription of new antihypertensive agents. There is a distinct lack of short-term and long-term CV and renal outcome studies on nurse-led hypertension care. However, an improvement in calculated CV and stroke risk has been seen in some studies looking at nurse-led hypertension clinics, and improvement in target organ damage such as left ventricular (LV) mass and left atrial (LA) volume changes, commonly affected by chronic hypertension, have been demonstrated in a

nurse-led community-based BP control study using a collaborative team approach in an underserved, high-risk population.

The DElay Future End-stage Nephropathy due to Diabetes (DEFEND) study was a novel, integrated model of care using a collaborative team approach of physician-nurse-healthcare assistant (HCA) to deliver home-based management of hypertension in Māori and Pacific patients with type 2 diabetes and established diabetic nephropathy.

The rationale for utilising HCAs in the study came from their role as cultural mediators to bridge the cultural gaps and to address the multitude of barriers that exist between the health service and Māori and Pacific communities. The language barrier was broken for the Tongan patients by our Tongan-speaking HCA. The HCAs acted as patient advocates, offering social and emotional support and an understanding of cultural values particular to their own ethnicity. They had a practical role in increasing the patient's access to health care by conducting home-based visits and providing transportation to the local pharmacy to collect prescribed medications and to the laboratory for blood and urine tests. They also promoted medication compliance in the community care (CC) patients.

The DEFEND study model of care led to a higher utilisation of antihypertensive medications in the CC patients at 12-months, with a decrease in mean systolic BP and a greater proportion of this group achieving target BP goals in comparison to the usual care (UC) group. The decrease in 24-hour urinary protein and a delayed progression in LV mass index (LVMI) and diastolic dysfunction seen in the CC group showed the effect of this model of care on target organ damage in patients with advanced renal disease and LV dysfunction. The improvements in the renal and CV parameters were compounded by the increase in both mean 24-hour urinary protein and a progression in LVMI and diastolic dysfunction in the conventional care group.

The DEFEND study applied many of the principles associated with increased effectiveness in achieving good BP control. Frequent BP monitoring, home-based visits, assistance with patient transport to and from study follow-up visits, and to the CC patient's local pharmacy to collect prescribed medications, removal of language and cultural barriers, and adherence to the medication protocol by the research staff were some of these factors. Given its simplistic framework, several components of this model of care could easily be applied into the community outpatient setting.

The DEFEND study was limited by difficulties in patient recruitment, resulting in a much smaller study than was initially anticipated. Recruitment numbers would likely have been higher if the criterion serum creatinine range had been wider, with the minimum threshold set at a lower value.

Early and regular screening for diabetes, hypertension, and nephropathy, and initiation of treatment in this patient population is mandatory for health outcomes to improve, and a clear benefit in CV risk reduction could be gained by patients being identified early on, with the initiation of treatment aiming to prevent the onset of cardiac or renal end-organ damage. While studies have shown that the use of RAAS blocking agents in patients with diabetes can result in regression of LVH and improvement in CV outcomes,[94,262,263] the BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) study showed that angiotensin converting enzyme (ACE) inhibition could significantly reduce the incidence of LVH in patients with type 2 diabetes and hypertension, advocating the need for early treatment prior to the development of target organ damage.[264] The potential impact on health outcomes by this model of care could be large, given the heightened risk for both progression to ESRD and for CV morbidity and mortality in this patient population, and the scope for prevention or delay of progressive disease in these patients.

The DEFEND study patients had established CKD, and although improvements were seen in proteinuria levels, suggesting a delay in renal disease progression,

CKD remained an important CV risk factor in these patients. Therefore, the addition of other cardio-protective therapy such as lipid-lowering agents, anti-platelet agents, and the implementation of measures to stop smoking, lose weight and attain optimal glycaemic control cannot be over-emphasised in the quest to reduce future risk of renal and CV outcomes.

The hope for the future is that effective and acceptable nationwide and community strategies will be implemented to reduce levels of obesity and diabetes, reduce the incidence of smoking, screen early for diabetes, and for those already affected by the complications of these conditions, to be able to offer effective and appropriate healthcare delivery that leads to a delay and even reversal of the processes leading to CV and renal disease progression.

References

1. Brougham A, Reed A, Karetu T. Reed book of Māori proverbs. Raupo Publishing (NZ) Ltd; Auckland 1992.
2. Hotu C, Bagg W, Collins J, et al. A community-based model of care improves blood pressure control and delays progression of proteinuria, left ventricular hypertrophy and diastolic dysfunction in Māori and Pacific patients with type 2 diabetes and chronic kidney disease: a randomised controlled trial. Nephrol Dial Transpl 2010;25:3260-6.
3. Pomare M, ed. Legends of the Māori. Southern Reprints; Auckland 1930.
4. ANZDATA Registry Report 2011. Australia and New Zealand Transplant and Dialysis Registry Adelaide, South Australia 2011.
5. Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases. Part I: General considerations, the epidemiologic transition, risk factors and impact of industrialisation. Circulation 2001;104:2746-53.
6. Sen K, Bonita R. Global health status: two steps forward, one step back. Lancet 2000;356:577-82.
7. Zimmet P, Alberti K, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782-7.
8. Historical population estimates. Statistics New Zealand. Wellington 2010.
9. Meredith P. Urban Māori – Urbanisation: Te Ara – the Encyclopedia of New Zealand; 2009.
10. King M. The Penguin History of New Zealand: Penguin; Auckland 2004.
11. Pacific mobility in New Zealand: Statistics New Zealand. Wellington 2010.
12. Asian mobility in New Zealand: Statistics New Zealand. Wellington 2010.
13. 2006 Census: Quickstats about New Zealand's population and dwellings. Statistics New Zealand. Wellington 2006.
14. Demographics of New Zealand's Pacific population. Statistics New Zealand and Ministry of Pacific Island Affairs. Wellington 2010.
15. Demographic aspects of New Zealand's ageing population. Statistics New Zealand. Wellington 2006.

16. Obesity: preventing and managing the global epidemic: Report of a WHO consultation. WHO Technical Report Series World Health Organisation Geneva 2000;894:8-9.
17. Obesity in New Zealand. Ministry of Health. Wellington 2009.
18. A Portrait of Health: Key results of the 2006/2007 New Zealand Health Survey. Ministry of Health. Wellington 2008.
19. Bell A, Swinburn B, Simmons D, et al. Heart disease and diabetes risk factors in Pacific Islands communities and associations with measures of body fat. N Z Med J 2001;114:364-5.
20. NZ Food, NZ Children: findings of the 2002 National Children's Nutrition Survey. Ministry of Health. Wellington 2003.
21. Tyrell V, Richards G, Hofman P, et al. Obesity in Auckland school children: a comparison of the body mass index and percentage body fat as the diagnostic criterion. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 2001;25:164-9.
22. Joshy G, Simmons D. Epidemiology of diabetes in New Zealand: Revisit to a changing landscape N Z Med J 2006;119:U1999.
23. Moore M, Lunt H. Diabetes in New Zealand. Diab Res Clin Pract 2000: S65-S71.
24. Taking the Pulse – The 1996/1997 New Zealand Health Survey. Ministry of Health. Wellington 1999.
25. A Portrait of Health: Key results of the 2002/2003 New Zealand Health Survey. Ministry of Health. Wellington 2004.
26. Simmons D, Harry T, Gatland B. Prevalence of known diabetes in different ethnic groups in inner urban South Auckland. N Z Med J 1999;112:116-9.
27. Simmons D. The epidemiology of diabetes and its complications in New Zealand. Diabetic Medicine 1996;13:371-5.
28. Simmons D, Fleming C. Prevalence and characteristics of diabetic patients with no ongoing care in South Auckland. Diabetes Care 2000;23:1791-3.

29. Simmons D, Gatland B, Leakehe L, et al. Frequency of diabetes in family members of probands with non-insulin dependent diabetes. J Int Med 1995;237:315-21.

30. Simmons D, Thompson C. Prevalence of the metabolic syndrome among adult New Zealanders of Polynesian and European descent. Diabetes Care 2004 27:3002-4.

31. Scragg R, Baker J, Metcalf P, et al. Prevalence of diabetes mellitus and impaired glucose tolerance in a New Zealand multiracial workforce. N Z Med J 1991;104:395-7.

32. Sundborn G, Metcalf P, Scragg R, et al. Ethnic differences in the prevalence of new and known diabetes mellitus, impaired glucose tolerance, and impaired fasting glucose. Diabetes Heart and Health Survey 2002-2003, Auckland, New Zealand. N Z Med J 2007;120:U2607.

33. Joshy G, Porter T, Le Lievre C, et al. Prevalence of diabetes in New Zealand General Practice: the influence of ethnicity and social deprivation. J Epidemiol Community Health 2009;63:386-90.

34. Simmons D. Diabetes detection on the surgical wards in an area with a high prevalence of diabetes. N Z Med J 1993;106:156-7.

35. Tipene-Leach D, Pahau H, Joseph N, et al. Insulin resistance in a rural Māori community N Z Med J 2004;117:U1208.

36. Simmons D, Rush E, Crook N, et al. Prevalence of undiagnosed diabetes, impaired glucose tolerance, and impaired fasting glucose among Māori in Te Wai O Rona: Diabetes Prevention Strategy. N Z Med J 2009;122:30-8.

37. Pierce M, Zaninotto P, Steel N, et al. Undiagnosed diabetes: becoming a thing of the past? Data from the English Longitudinal Study of Ageing and the Health Survey for England. Diabetologia 2007;50:S35.

38. Rosenbloom A, Joe J, Young R, et al. Emerging epidemic of type 2 diabetes in youth. Diabetes Care 1999;22:345-54.

39. American Diabetes Association: Type 2 diabetes in children and adolescents. Diabetes Care 2000;23:381-9.

40. Hotu S, Carter B, Watson P, et al. Increasing prevalence of type 2 diabetes in adolescents. Journal of Paediatrics & Child Health 2004;40:201-4.

41. McGrath N, Parker G, Dawson P. Early presentation of type 2 diabetes mellitus in young New Zealand Māori. Diab Res Clin Pract 1999;43:205-9.

42. Scott A, Whitcombe S, Bouchier D, et al. Diabetes in children and young adults in Waikato province, New Zealand: outcomes of care. N Z Med J 2004;117:U1219.

43. Ministry of Health: Diabetes Care Improvement Package. NZ Ministry of Health. Wellington 2012.

44. Tomlin A, Tilyard M, Dawson A, et al. Health status of New Zealand European, Māori, and Pacific patients with diabetes in 242 New Zealand general practices. N Z Med J 2006;19:U2004.

45. Modelling diabetes: A summary. NZ Ministry of Health. Wellington 2002.

46. Simmons D, Clover G, Hope C. Ethnic differences in diabetic retinopathy. Diabet Med 2007;24:1093-8.

47. Simmons D, Scott D, Kenealy T, et al. Foot care among diabetes patients in South Auckland. N Z Med J 1995;108:106-8.

48. Joshy G, Colonne C, Dunn P, et al. Ethnic disparities in causes of death among diabetes patients in the Waikato region of New Zealand. N Z Med J 2010;123.

49. Simmons D, Schaumkel J, Cecil A, et al. High impact of nephropathy on five-year mortality rates among patients with type 2 diabetes mellitus from a multi-ethnic population in New Zealand. Diabet Med 1999;16:926-31.

50. Jeffreys M, Wright C, 't Mannetje A, et al. Ethnic differences in cause specific mortality among hospitalised patients with diabetes: a linkage study in New Zealand. J Epidemiol Community Health 2005;59:961-6.

51. Sarnak M, Levey A, Schoolwerth A, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention. Hypertension 2003;42:1050-65.

52. American Diabetes Association Position Statement: Nephropathy in Diabetes. Diabetes Care 2004:S79-S83.

53. Viberti G, Bilous R, Mackintosh D, et al. Monitoring glomerular function in diabetic nephropathy: a prospective study. Am J Med 1983;74:256-64.

54. Radbill B, Murphy B, LeRoith D. Rationale and strategies for early detection and management of diabetic kidney disease. Mayo Clin Proc 2008;83:1373-81.

55. Chaturvedi N, Bandinelli S, Mangili R, on behalf of the EURODIAB Prospective Complications Study Group. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. Kidney Int 2001;60:219-27.

56. The Microalbuminuria Collaborative Study Group. Predictors of the development of microalbuminuria in patients with type 1 diabetes mellitus: a seven year prospective study. Diabet Med 1999;16:918-25.

57. Adler A, Stevens R, Manley S, on behalf of the UKPDS Group. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225-32.

58. Murussi M, Baglio P, Gross J, et al. Risk factors for microalbuminuria and macroalbuminuria in type 2 diabetic patients – a 9-year follow-up study. Diabetes Care 2002;25:1101-3.

59. Caramori M, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? . Diabetes 2000;49:1399-408.

60. Alzaid A. Microalbuminuria in patients with NIDDM: an overview. Diabetes Care 1996;19:79-89.

61. Viberti G, Hill R, Jarrett R, et al. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1:1430-2.

62. Mogensen C, Christiansen C. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 1984;311:89-93.

63. Mauer S, Steffes M, Brown D. The kidney in diabetes. Am J Med 1981;70:603-12.

64. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007;27:195-207.

65. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. Diabetologia 1996;39:1569-76.

66. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis 2007;49:S1-S180.

67. Stephenson J, Fuller J. Microalbuminuria is not rare before 5 years of IDDM: EURODIAB IDDM Complications Study Group and the WHO Multinational Study of Vascular Disease in Diabetes Study Group. J Diabetes Complications 1994;8:166-73.

68. Schultz C, Konopelska-Bahu T, Dalton R, et al. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study: Oxford Regional Prospective Study Group. Diabetes Care 1999;22:495-502.

69. Mogensen C, Vestbo E, Poulsen P, et al. Microalbuminuria and potential confounders: a review and some observations on variability of urinary albumin excretion. Diabetes Care 1995;18:572-81.

70. US Renal Data System: USRDS 2010 Annual Data Report: 2010 Atlas of End-Stage Renal Disease in the United States. National Institute of

Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethseda, MD 2010.

71. Gall M, Hougaard P, Borch-Johnsen K, et al. Risk factors for development of incipient or overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus:prospective, observational study. BMJ 1997;314:783-8.

72. Ravid M, Brosh D, Ravid-Safran D, et al. Main risk factors for nephropathy in type 2 diabetes are plasma cholesterol levels, mean blood pressure, and hyperglycaemia. Arch Intern Med 1998;158:998-1004.

73. Singh R, Barden A, Mori T, et al. Advanced glycation end-products: a review. Diabetologia 2001;44:129-46.

74. Chen S, Jim B, Ziyadeh F. Diabetic nephropathy and transforming growth factor-beta: transforming our view of glomerulosclerosis and fibrosis build-up. Semin Nephrol 2003;23:532-43.

75. Steffes M, Sutherland D, Goetz F, et al. Studies of kidney and muscle biopsy specimens from identical twins discordant for type 1 diabetes mellitus. N Engl J Med 1985;312:1282-7.

76. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl Med J 1993;329:977-86.

77. Stratton I, Adler A, Neil H, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

78. Adler A, Stratton I, Neil H, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412-9.

79. Nørgaard K, Feldt-Rasmussen B, Borch-Johnsen K, et al. Prevalence in hypertension in Type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1990:407-10.

80. Lurbe E, Redon J, Kesani A, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 2002;347:797-805.

81. Palatini P, Mormino P, Dorigatti F, et al. Glomerular hyperfiltration predicts the development of microalbuminuria in stage 1 hypertension: the HARVEST. Kidney Int 2006;70:578-84.

82. Magee G, Bilous R, Cardwell C, et al. Is hyperfiltration associated with future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia 2009;52:691-7.

83. Nelson R, Bennett P, Beck G, et al. Development and progression of renal disease in Pima Indians with non-insulin dependent diabetes mellitus. N Engl J Med 1996;335:1636-42.

84. Chase P, Garg S, Marshall G, et al. Cigarette smoking increases the risk of albuminuria among subjects with type 1 diabetes. JAMA 1991;265:614-7.

85. Gambaro G, Bax G, Fusaro M, et al. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. Diabetes, Nutrition & Metabolism 2001;14:337-42.

86. Scott L, Warram J, Hanna L, et al. A nonlinear effect of hyperglycaemia and cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. Diabetes 2001;50:2842-9.

87. Harjutsalo V, Kato S, Sarti C, et al. Population-based assessment of familial clustering of diabetic nephropathy in type 1 diabetes. Diabetes 2004;53:2449-54.

88. Pettitt D, Saad M, Bennett P, et al. Familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1990;33:438-43.

89. Seaquist E, Goetz F, Rich S, et al. Familial clustering of diabetic kidney disease. N Engl J Med 1989;320:1161-5.

90. Hillege H, Fidler V, Diercks G, on behalf of the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin

excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002;106:1777-82.

91. Yuyun M, Khaw K, Luben R, et al. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Int J Epidem 2004;33:189-98.
92. Mogensen C. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310:356-60.
93. Dinneen S, Gerstein H. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systematic review of the literature. Arch Intern Med 1997;157:1413-8.
94. Gerstein H, Yusuf S, Mann J, on behalf of the Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9.
95. Gerstein H, Mann J. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421-6.
96. Go A, Chertow G, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalisation. N Engl J Med 2004;351:1296-305.
97. Muntner P, He J, Hamm L, et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002;13:745-53.
98. Shulman N, Ford C, Hall W, on behalf of the Hypertension Detection and Follow-up Program Cooperative Group. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function Results from the hypertension detection and follow-up program. Hypertension 1989;13: I80-I93.

99. Foley R, Parfrey P, Sarnak M. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9:S16-S23.

100. Tonelli M, Bohm C, Pandeya S, et al. Cardiac risk factors and use of cardioprotective medications in patients with chronic renal insufficiency. Am J Kidney Dis 2001;37:484-9.

101. Foley R, Parfrey P, Harnett J, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995;47:186-92.

102. Harnett J, Foley R, Kent G, et al. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int 1995;47:884-90.

103. Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant 2000;15:218-23.

104. Stehouwer C, Zeldenrust G, den Ottolander G, et al. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet 1992;340:319-23.

105. Lunt H, Lim C, Crooke M, et al. Comparison of urinary albumin excretion between Māoris, Pacific Island Polynesians and Europeans with non-insulin-dependent diabetes. Diab Res Clin Pract 1990;8:45-50.

106. Stewart J, McCredie M, McDonald S. The incidence of treated end-stage renal disease in New Zealand Māori and Pacific Island people and in Indigenous Australians. Nephrol Dial Transplant 2004;19:678-85.

107. McDonald S, Russ G. Burden of end-stage renal disease among indigenous peoples in Australia and New Zealand. Kidney Int 2003;63:S123-7.

108. McDonald S, Russ G. Current incidence, treatment patterns and incidence of end-stage renal disease among indigenous groups in Australia and New Zealand. Nephrology 2003;8:42-8.

109. Joshy G, Dunn P, Fisher M, et al. Ethnic differences in the natural progression of nephropathy among diabetes patients in NZ: hospital admission rate for renal complications, and incidence of end-stage renal disease and renal death. Diabetologia 2009;52:1474-8.

110. Bruce R, Williams L, Cundy T. Rates of progression to end stage renal failure in nephropathy secondary to type 1 and type 2 diabetes mellitus. Aust NZ J Med 1994;24:390-5.

111. Simmons D, Shaw L, Scott D, et al. Diabetic nephropathy and microalbuminuria in the community. The South Auckland Diabetes Survey. Diabetes Care 1994;17:1404-10.

112. Lim S, Chellumuthi C, Crook N, et al. Low prevalence of retinopathy, but high prevalence of nephropathy among Māori with newly diagnosed diabetes – Te Wai O Rona: diabetes prevention strategy. Diab Res Clin Pract 2008;80:271-4.

113. Thompson C, Simmons D, Collins J, et al. Predisposition to nephropathy in Polynesians is associated with family history of renal disease, not diabetes mellitus. Diabet Med 2001;18:40-6.

114. Price Waterhouse Coopers, Commissioned by Diabetes New Zealand Inc. Type 2 diabetes – outcomes model update 2007.

115. Endre Z, Beaven D, Buttimore A. Preventable kidney failure: the cost of diabetes neglect. N Z Med J 2006;119:22-9.

116. ANZDATA Registry Report 2004. Australia and New Zealand Transplant and Dialysis Registry Adelaide, South Australia 2004.

117. The Quit Group and the Ministry of Health. Māori smoking and tobacco use. Wellington; 2009.

118. Braatvedt G, Rosie B, Bagg W, et al. Current and former smoking increases mortality in patients on peritoneal dialysis. N Z Med J 2006;119:U1977.

119. Parving H, Smidt U, Andersen A, et al. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. Lancet 1983;1:1175-9.

120. Lewis E, Hunsicker L, Bain R, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456-62.

121. Patel A, MacMahon S, Chalmers J, on behalf of the ADVANCE Collaborative Group. Effects of a fixed combination of perinodopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829-40.

122. Parving H, Lehnert H, Bröchner-Mortensen J, on behalf of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.

123. Brenner B, Cooper M, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.

124. De Zeeuw D, Remuzzi G, Parving H, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65:2309-20.

125. Lewis E, Hunsicker L, Clarke W, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.

126. Lacourcière Y, Bélanger A, Godin C, et al. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. Kidney Int 2000;58:762-9.

127. Barnett A, Bain S, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952-61.

128. CALM Study Group. Randomised controlled trial of dual blockade of renin- angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000;321:1440-4.

129. Jacobsen P, Rossing K, Parving H, et al. Single versus dual blockade of the renin angiotensin system (angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers) in diabetic nephropathy. Curr Opin Nephrol Hypertens 2004;13:319-24.

130. Rossing K, Christensen P, Jensen B, et al. Dual blockade of the renin angiotensin system in diabetic nephropathy: a randomised double blind cross over study. Diabetes Care 2002;25:95-100.

131. Yusuf S, Sleight P, Anderson C, on behalf of The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.

132. Schjoedt K, Rossing K, Juhl T, et al. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. Kidney Int 2006;70:536-42.

133. Rachmani R, Slavachevsky I, Amit M, et al. The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomised controlled study. Diabet Med 2004;21:471-5.

134. Rossing K, Schjoedt K, Smidt U, et al. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomised, double-masked, cross-over study. Diabetes Care 2005;28:2106-12.

135. Mehdi U, Adams-Huet B, Raskin P. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol 2009;20:2641-50.

136. Bakris G, Copley J, Vicknair N, et al. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 1996;50:1641-50.

137. Hansson L, Zanchetti A, Carruthers S, on behalf of the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-62.

138. Turner R, Holman R, Stratton I, on behalf of the UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.

139. Cushman W, Evans G, Byington R, on behalf of the Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive blood-pressure control in type 2 diabetes. N Engl J Med 2010;362:1575-85.

140. American Diabetes Association Position Statement: Standards of Medical Care in Diabetes - 2011. Diabetes Care 2011;34:S11-S61.

141. Chobanian A, Bakris G, Black H, on behalf of the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289:2560-72.

142. American Diabetes Association Position Statement: Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26:S80-S2.

143. Berlowitz D, Ash A, Hickey E, et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med 1998;339:1957-63.

144. Mancia G, Sega R, Milesi C, et al. Blood pressure control in the hypertensive population. Lancet 1997;349:454-7.

145. Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: can we fill the gap? J Hypertension 2002;20:1251-3.

146. Hajjar I, Kotchen T. Trends in awareness, prevalence, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003;290:199-206.

147. Clark C, Smith L, Tayor R, et al. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. BMJ 2010;341:1-17.

148. Phillips L, Branch W, Cook C, et al. Clinical Inertia. Ann Intern Med 2001;135:825-34.

149. Byrnes P. Why haven't I changed that? Therapeutic inertia in general practice. Aust Fam Physician 2011;40:24-8.

150. Oliveria S, Lapuerta P, McCarthy B, et al. Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med 2002;162:413-20.

151. Borzecki A, Oliveria S, Berlowitz D. Barriers to hypertension control. Am Heart J 2005;149:785-94.

152. O'Brien E, Asmar R, Beilin L, on behalf of the European Society of Hypertension working group on blood pressure monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertension 2003;21:821-48.

153. Stergiou G, Mengden T, Padfield P, et al. Self monitoring of blood pressure at home. BMJ 2004;329:870-1.

154. Ohkubo T, Imai Y, Tsuji I, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertension 1998;16:971-5.

155. McManus R, Rant J, Roalfe A, et al. Targets and self monitoring in hypertension: a randomised controlled trial and cost-effectiveness analysis. BMJ 2005;331:466-7.

156. Cappuccio F, Kerry S, Forbes L, et al. Blood pressure control by home monitoring: meta-analysis of randomised trials. BMJ 2004;329:145-8.

157. Artinian N, Flack J, Nordstrom C, et al. Effects of nurse-managed telemonitoring on blood pressure at 12-month follow-up among urban African Americans. Nurs Res 2007;56:312-22.

158. Bosworth H, Olsen M, Grubber J, et al. Two self-management interventions to improve hypertension control: a randomised trial. Ann Int Med 2009;151:687-95.

159. Logan A, Milne B, Achber C, et al. Work-site treatment of hypertension by specially trained nurses. Lancet 1979:1175-8.

160. Denver E, Barnard M, Woolfson R, et al. Management of uncontrolled hypertension in a nurse-led clinic compared to conventional care for patients with type 2 diabetes. Diabetes Care 2003;26:2256-60.

161. Horrocks S, Anderson E, Salisbury C. Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. BMJ 2002;324:819-23.

162. Oakeshott P, Kerry S, Austin A, et al. Is there a role for nurse-led blood pressure management in primary care? Family Practice 2003;20:469-73.

163. Schroeder K, Fahey T, Hollinghurst S, et al. Nurse-led adherence support in hypertension: a randomised controlled trial. Family Practice 2005;22:144-51.

164. Vivian E. Improving blood pressure control in a pharmacist-managed hypertension clinic. Pharmacotherapy 2002;22:1533-40.

165. Kelly C, Booth G. Pharmacist-led structured care for patients with diabetic nephropathy. Br J Diab Vasc Dis 2006;8:86-8.

166. Carter B, Bergus G, Dawson J, et al. A cluster-randomised trial to evaluate physician/pharmacist collaboration to improve blood pressure control. J Clin Hypertens 2008;10:260-71.

167. Carter B, Ardery G, Dawson J, et al. Physician and pharmacist collaboration to improve blood pressure control. Arch Intern Med 2009;169:1996-2002.

168. Lee J, Grace K, Taylor A. Effect of a pharmacy care program on medication adherence and persistence, blood pressure and low-density lipoprotein cholesterol. JAMA 2006;296:2563-71.

169. Reid F, Murray P, Storrie M. Implementation of a pharmacist-led clinic for hypertensive patients in primary care – a pilot study. Pharm World Sci 2005;27:202-7.

170. McLean D, McAlister F, Johnson J, et al. A randomised trial of the effect of community pharmacist and nurse care on improving blood pressure management in patients with diabetes mellitus: study of cardiovascular risk intervention by pharmacists-hypertension (SCRIP-HTN). Arch Intern Med 2008;168:2355-61.

171. Sookaneknun P, Richards R, Sanguansermsri J, et al. Pharmacist involvement in primary care improves hypertensive clinical outcomes. Ann Pharmacother 2004;38:2023-8.

172. Krieger J, Collier C, Song L, et al. Linking community-based blood pressure measurement to clinical care: a randomised controlled trial of outreach and tracking by community health workers. Am J Pub Health 1999;89:856-61.

173. Hill M, Han H, Dennison C, et al. Hypertension care and control in underserved urban African American men: behavioural and physiologic outcomes at 36 months. Am J Hypertension 2003;16:906-13.

174. Hypertension Detection and Follow-Up Program Cooperative Group. The Hypertension Detection and Follow-Up Program. Prev Med 1976;5:207-15.

175. Hypertension Detection and Follow-Up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-Up Program. Reduction in mortality in persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562-71.

176. Glynn L, Murphy A, Smith S, et al. Interventions to improve control of blood pressure in patients with hypertension. Cochrane Database of Systemic Reviews 2010.

177. Campbell N, Ritchie L, Thain J, et al. Secondary prevention in coronary heart disease: a randomised trial of nurse led clinics in primary care. Heart 1998;80:447-52.

178. McHugh F, Lindsay G, Hanlon P, et al. Nurse led shared care for patients on the waiting list for coronary artery bypass surgery: a randomised controlled trial. Heart 2001;86:317-23.

179. Rudd P, Miller N, Kaufman J, et al. Nurse management for hypertension. A systems approach. Am J Hypertension 2004;17:921-7.

180. Becker D, Yanek L, Johnson W, et al. Impact of a community-based multiple risk factor intervention on cardiovascular risk in Black families with a history of premature coronary disease. Circulation 2005;111:1298-304.

181. Woodward A, Wallymahmed M, Wilding J, et al. Successful cardiovascular risk reduction in type 2 diabetes by nurse-led care using an open clinical algorithm. Diab Med 2006;23:780-7.

182. Mugarza J, Wilding J, Woodward A, et al. Achieving blood pressure control in patients with type 2 diabetes and diabetic renal disease by a nurse-led protocol based clinic. Brit J Diab Vasc Dis 2008;8:279-84.

183. Pearson A, Gudipati C, Nagelhout D, et al. Echocardiographic evaluation of cardiac structure and function in elderly subjects with isolated systolic hypertension. J Am Coll Cardiol 1991;17:422-30.

184. Levy D, Garrison R, Savage D, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561-6.

185. Verdecchia P, Schillaci G, Borgioni C, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation 1998;97:48-54.

186. Masding M, Jones J, Bartley E, et al. Assessment of blood pressure in patients with type 2 diabetes: comparison between home blood pressure monitoring, clinic blood pressure measurement and 24-h ambulatory blood pressure monitoring. Diabet Med 2001;18:431-7.

187. Amar J, Vernier I, Rossignol E, et al. Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. Kidney Int 2000;57:2485-91.

188. Nakano S, Fukuda M, Hotta F, et al. Reversed circadian blood pressure rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects. Diabetes 1998;47:1501-6.

189. Nakano S, Konishi K, Furuya K, et al. A prognostic role of mean 24-h pulse pressure level for cardiovascular events in type 2 diabetic subjects under 60 years of age. Diabetes Care 2005;28:95-100.

190. McGrath B. Ambulatory blood pressure monitoring. Med J Aust 2002;176:588-92.

191. Staessen J, Fagard R, Lijnen P, et al. Mean and range of the ambulatory pressure in normotensive subjects from a meta-analysis of 23 studies. Am J Cardiol 1991;67:723-7.

192. Staessen J, O'Brien E, Atkins N, et al. Ambulatory blood pressure in normotensive compared with hypertensive subjects. J Hypertension 1993;11:1289–97.

193. Imai Y, Nagai K, Sakuma M, et al. Ambulatory blood pressure of adults in Ohasama, Japan. Hypertension 1993;22:900-12.

194. Hansen T, Kikuya M, Thijs L, et al. Diagnostic thresholds for ambulatory blood pressure moving lower: a review based on a meta-analysis - clinical implications. J Clin Hypertens 2008;10:377-81.

195. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. JAMA 1983;249:2792-8.

196. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure – an independent predictor of prognosis in essential hypertension. Hypertension 1994;24:793-801.

197. Ohkubo T, Imai Y, Nagai K, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. J Hypertension 1997;15:357-64.

198. Redon J, Campos C, Narciso M, et al. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. Hypertension 1998;31:712-8.

199. Staessen J, Thijs L, Fagard R. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. JAMA 1999;282:539-46.

200. Kario K, Shimada K, Schwartz J, et al. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. J Am Coll Cardiol 2001;38:238-45.

201. Mancia G, Sega R, Bravi C, et al. Ambulatory blood pressure normality: results from the PAMELA study. J Hypertens 1995;13:1377-90.

202. O'Brien E, Asmar R, Beilin L, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. J Hypertension 2005;23:697-701.

203. Pickering T, Hall J, Appel L, et al. Recommendations for blood pressure measurement in humans and experimental animals. Circulation 2005;111:697-716.

204. Pickering T, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med 2006;354:2368-74.

205. Fogari R, Zoppi A, Malamani G, et al. Ambulatory blood pressure monitoring in normotensive and hypertensive type 2 diabetes. Prevalence of impaired diurnal blood pressure patterns. Am J Hypertension 1993;6:1-7.

206. Marczewski K, Krawczyk W, Rózyc G, et al. Day/night ratio of microproteinuria and blood pressure rhythm in type II diabetes. Diab Res Clin Pract 1996;33:169-72.

207. Equiluz-Bruck S, Schnack C, Kopp H, et al. Nondipping of nocturnal blood pressure is related to urinary albumin excretion rate in patients with type 2 diabetes mellitus. Am J Hypertension 1996;9:1139-43.

208. Torffvit O, Tapia J, Rippe B, et al. Ambulatory blood pressure in type 2 diabetic patients with albuminuria: relation to the renal function and structural lesions. J Diabetes Complications 2004;18:328-35.

209. Lurbe A, Redon J, Pascual J, et al. Altered blood pressure during sleep in normotensive subjects with type 1 diabetes. Hypertension 1993;21:227-35.

210. Poulsen P, Hansen K, Mogensen C. Ambulatory blood pressure in the transition from normo- to microalbuminuria: a longitudinal study in IDDM patients. Diabetes 1994;43:1248-53.

211. Voros P, Lengyel Z, Nagy V, et al. Diurnal blood pressure variation and albuminuria in normotensive patients with insulin-dependent diabetes mellitus. Nephrol Dial Transpl 1998;13:2257-60.

212. Nielsen S, Schmitz A, Poulsen P, et al. Albuminuria and 24-h ambulatory blood pressure in normoalbuminuric and microalbuminuric NIDDM patients. A longitudinal study. Diabetes Care 1995;18:1434-41.

213. Chau N, Bauduceau B, Chanudet X, et al. Ambulatory blood pressure in diabetic subjects. Am J Hypertension 1994;7:487-91.

214. Farmer C, Goldsmith D, Cox J, et al. An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variablility. Nephrol Dial Transpl 1997;12:2301-7.

215. Mitsnefes M, Kimball T, Daniels S. Office and ambulatory blood pressure elevation in children with chronic renal failure. Pediatr Nephrol 2003;18:145-9.

216. Timio M, Venanzi S, Lolli S, et al. “Non-dipper” hypertensive patients and progressive renal insufficiency: a 3-year longitudinal study. Clin Nephrol 1995;43:382-7.

217. Cohen C, Filho F, Goncalves M, et al. Early alterations of blood pressure in normotensive and normoalbuminuric type 1 diabetic patients. Diab Res Clin Pract 2001;53:85-90.

218. Keller C, Bergis K, Fliser D, et al. Renal findings in patients with short-term type 2 diabetes. J Am Soc Nephrol 1996;7:2627-35.

219. Bauduceau B, Genes N, Chamontin B, et al. Ambulatory blood pressure and urinary albumin excretion in diabetic (non-insulin-dependent and insulin-dependent) hypertensive patients: relationships at baseline and after treatment by the angiotensin converting enzyme inhibitor trandolapril. Am J Hypertension 1998;11:1065-73.

220. Paoletti E, Bellino D, Amidone M, et al. Relationship between arterial hypertension and renal damage in chronic kidney disease: insights from ABPM. J Nephrol 2006;19:778-82.

221. Toth L, Voros P, Lengyel Z, et al. Diurnal blood pressure variations in incipient and end stage diabetic renal disease. Diab Res Clin Pract 2000;49:1-6.

222. Hornung R, Mahler R, Raftery E. Ambulatory blood pressure and heart rate in diabetic patients: an assessment of autonomic function. Diabet Med 1989;6:579-85.

223. Ikeda T, Matsubara T, Sato Y, et al. Circadian blood pressure variation in diabetic patients with autonomic neuropathy. J Hypertension 1993;11:581-7.

224. Kondo K, Matsubara T, Nakamura J, et al. Characteristic patterns of circadian variation in plasma catecholamine levels, blood pressure and heart rate variability in type 2 diabetic patients. Diabetic Medicine 2002;19:359-65.

225. Moran A, Palmas W, Field L, et al. Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes. Diabetes Care 2004;27:972-7.

226. Wolf J, Hering D, Narkiewicz K. Non-dipping of hypertension and obstructive sleep apnoea. Hypertens Res 2010;33:867-71.

227. Tedla F, Brar A, Browne R, et al. Hypertension in chronic kidney disease: navigating the evidence. Int J Hypertens 2011;2011.

228. Steigerwalt S. Management of hypertension in diabetic patients with chronic kidney disease. Diab Spectrum 2008;21:30-6.

229. White W, Schulman P, McCabe E, et al. Average daily blood pressure, not office pressure, determines cardiac function in patients with hypertension. JAMA 1989;261:873-7.

230. Parati G, Pomidossi G, Albini F, et al. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. J Hypertension 1987;5:93-8.

231. Verdecchia P, Schillaci G, Guerrieri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528-36.

232. Tucker B, Fabbian F, Giles M, et al. Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. Nephrol Dial Transpl 1997;12:724-8.

233. Rahman M, Griffin V, Hevka R, et al. Diurnal variation of blood pressure; reproducibility and association with left ventricular hypertrophy in hemodialysis patients. Blood Press Monit 2005;10:25-32.

234. Fagugli R, Quintaliani G, Pasini P, et al. Blunted nocturnal blood pressure decrease and left-ventricular mass in hypertensive hemodialysis patients. Nephron 2002;91:79-85.

235. Mancia G, Zanchetti A, Agabiti-Rosei E, et al. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE study group. Study

on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation. Circulation 1997;95:1464-70.

236. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality. The Dublin Outcome Study. Hypertension 2005;46:156-61.
237. Clement D, De Buyzere M, De Bacquer D, et al. Prognostic value of ambulatory blood pressure recordings in patients with treated hypertension. N Engl J Med 2003;348:2407-15.
238. Sturrock N, George E, Pound N, et al. Non-dipping circadian blood pressure and renal impairment are associated with increased mortality in diabetes. Diabetic Medicine 2000;17:360-4.
239. Boggia J, Liu Y, Thijs L, et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet 2007;370:1219-29.
240. Fagard R, Thijs L, Staessen J, et al. Night-day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens 2009;23:645-53.
241. Verdecchia P, Schillaci G, Borgioni C, et al. Ambulatory pulse pressure: a potent predictor of total cardiovascular risk in hypertension. Hypertension 1998;32:983-8.
242. Liu M, Takahashi H, Morita Y, et al. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. Nephrol Dial Transpl 2003;18:563-9.
243. Knudsen S, Laugesen E, Hansen K, et al. Ambulatory pulse pressure, decreased nocturnal blood pressure reduction and progression of nephropathy in type 2 diabetic patients. Diabetologia 2009;52:698-704.
244. Farmer C, Goldsmith D, Quin J, et al. Progression of diabetic nephropathy – is diurnal blood pressure rhythm as important as absolute blood pressure level? Nephrol Dial Transpl 1998;13:635-9.

245. Agarwal R, Andersen M. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int 2006;69:1175-80.

246. Minutolo R, Agarwal R, Borrelli S, et al. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. Arch Intern Med 2011;171:1090-8.

247. Baxter J. Barriers to health care for Māori with known diabetes. Te Roopu Rangahau Hauora a Ngai Tahu 2002.

248. Nand K, Collins J. Audit of Auckland patients with end-stage renal disease secondary to type 2 diabetes. Auckland 2002.

249. New Zealand Guidelines Group, ed. Management of type 2 diabetes. Wellington: New Zealand Guidelines Group; 2003.

250. Lang R, Bierig M, Devereus R, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee, and the Chamber, Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

251. Paoletti E, Bellino D, Gallina A, et al. Is left ventricular hypertrophy a powerful predictor of progression to dialysis in chronic kidney disease? Nephrol Dial Transpl 2011;26:670-7.

252. Verdecchia P, Carini G, Circo A, et al. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. J Am Coll Cardiol 2001;38:1829-35.

253. Verdecchia P, Porcellati C, Reboldi G. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. Circulation 2001;104:2039-44.

254. Redfield M, Jacobsen S, Burnett J, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194-202.

255. AlJaroudi W, Alraies M, Halley C, et al. Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. Circulation 2012;125:782-8.

256. Chen S, Su H, Hung C, et al. Echocardiographic parameters are independently associated with rate of renal function decline and progression to dialysis in patients with chronic kidney disease. Clin J Am Soc Nephrol 2011;6:2750-8.

257. Russo C, Jin Z, Homma S, et al. Effect of diabetes and hypertension on left ventricular diastolic function in a high-risk population without evidence of heart disease. Eur J Heart Fail 2010;12:454-61.

258. Verdecchia P, Angeli F, Borgioni C, et al. Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: a meta-analysis. Am J Hypertens 2003;16:895-9.

259. Pierdomenico S, Lapenna D, Cuccurullo F. Regression of echocardiographic left ventricular hypertrophy after 2 years of therapy reduces cardiovascular risk in patients with essential hypertension. Am J Hypertens 2008;21:464-70.

260. Hill A. The environment and disease: association or causation? Proc R Soc Med 1965;58:293-300.

261. O'Brien E, Coats A, Owens P, et al. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. BMJ 2000;320:1128-34.

262. Dahlöf B, Devereux R, Kjeldsen S, et al. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.

263. Lindholm L, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:1004-10.

264. Ruggenenti P, Iliev I, Costa G, et al. Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 diabetes. Diabetes Care 2008;31:1629-34.

Appendix A

DEFEND
Delay future end stage nephropathy due to diabetes

Form C: Follow-up Assessment
(Intensive Participants)

Participant initials ⌊⌊⌊⌊

Registration number ⌊⌊⌊ - ⌊⌊⌊

⌊⌊⌊⌊⌊⌊ Form ID
Complete after input of form

Affix registration label here

- Please complete Form C at each monthly visit if the participant has been randomised into the DEFEND trial (Intensive group).
- When completing CRF:
  - Write participant initials and registration number on every page of the form.
  - Answer all questions. DO NOT LEAVE BLANK SPACES.
  - Tick circles, write numbers in boxes.
  - If the data are unavailable put an asterisk '*'.
  - If the data are not applicable put a dash '-'.

1. Vital Status/Assessment Details

1.01 ⌊⌊ Month number (remember to use Form D for month 12 and Month 24)

1.02 ⌊⌊⌊⌊2⌊0⌊⌊ Date of assessment
day month year

1.03 ⌊⌊:⌊⌊ Start time (24 hour)
hh min

	Yes	No	
1.04	○	○	Patient alive on scheduled assessment date
1.05		→	**If No,** ⌊⌊⌊⌊2⌊0⌊⌊ date of death (ensure death is reported on Form x) *day month year*

→ **If Yes,**

	Yes	No	
1.06	○	○	Scheduled visit conducted
1.07		→	**If No**, reason for missed assessment (tick one only)

- ○ Patient unwell
- ○ Patient refused visit
- ○ Patient away/unavailable
- ○ Doctor's decision
- ○ Other reason

→ **If Yes**, complete rest of the form

1.08 Where did this visit occur (tick ONE only)

- ○ Home
- ○ Work
- ○ Clinic
- ○ Other

DEFEND
Delay future end stage nephropathy due to diabetes

Form C: Follow-up Assessment
(Intensive Participants)

Participant initials	Registration number
⌊⌊⌊⌊	⌊⌊⌊ - ⌊⌊⌊

Affix registration label here

1.09 ⌊⌊ Number of people present (excluding patient)

	Yes	No	
1.10	○	○	Was an Interpreter used?

2. Compliance with Current medication (estimated compliances)

		Good = Most of the time	Average = Missing some	Poor = hardly ever taking	N/A = not applicable
2.01	ACE Inhibitor	○	○	○	○
2.02	Calcium Channel Blocker	○	○	○	○
2.03	Beta Blocker	○	○	○	○
2.04	ARB	○	○	○	○
2.05	Diuretic	○	○	○	○
2.06	Alpha Blocker	○	○	○	○
2.07	Aspirin	○	○	○	○
2.08	Statins	○	○	○	○

	Yes	No	
2.09	○	○	Was the yellow medication card sighted
2.10	○	○	Was the patient medication sighted

3. Allergies, Intolerances and Contra-indications to Study medication (new since last visit)

		Allergic	Intolerant	Contra-indication	None	Unknown
3.01	ACE Inhibitor	○	○	○	○	○
3.02	Calcium Channel Blocker	○	○	○	○	○
3.03	Beta Blocker	○	○	○	○	○
3.04	ARB	○	○	○	○	○
3.05	Diuretic	○	○	○	○	○
3.06	Alpha Blocker	○	○	○	○	○
3.07	Aspirin	○	○	○	○	○
3.08	Statins	○	○	○	○	○

DEFEND
Delay future end stage nephropathy due to diabetes

Form C: Follow-up Assessment
(Intensive Participants)

Participant initials |_|_| |_|_|

Registration number |_|_| - |_|_|_|

Affix registration label here

3.09 Comments regarding study medication allergies, intolerances, contra-indications:

	Yes	No	
3.10	○	○	Any other new drug allergies?
3.11	→		**If Yes**, specify

4. Blood Pressure

Size of cuff used *(tick ONE only)*

4.01 ○ Standard
○ Large

Which arm used *(tick ONE only)*

4.02 ○ Left
○ Right

Blood pressure SBP/DBP

	Seated	Standing	
4.03	|_|_|_| / |_|_|_| *systolic mm/Hg* *diastolic mm/Hg*	|_|_|_| / |_|_|_| *systolic mm/Hg* *diastolic mm/Hg*	1 minute
4.04	|_|_|_| / |_|_|_| *systolic mm/Hg* *diastolic mm/Hg*	|_|_|_| / |_|_|_| *systolic mm/Hg* *diastolic mm/Hg*	2 minutes
4.05	|_|_|_| / |_|_|_| *systolic mm/Hg* *diastolic mm/Hg*		3 minutes
4.06	|_|_|_| / |_|_|_| *systolic mm/Hg* *diastolic mm/Hg*		Average seated BP (2 + 3)/2

Participant initials ⌊⌊⌊⌊

Registration number ⌊⌊⌊ - ⌊⌊⌊

Affix registration label here

Pulse rate

	Seated	Standing	
4.07	⌊⌊⌊	⌊⌊⌊	1 minute
4.08	⌊⌊⌊	⌊⌊⌊	2 minutes

4.09 Does the patient experience dizziness or light-headedness on standing? *(tick ONE only)*

- ○ None
- ○ Mild
- ○ Moderate
- ○ Severe

	Yes	No	
4.10	○	○	Does the SBP drop by more than 20mm/Hg on standing? If moderate or severe symptoms (Q4.09) and standing SBP ≤ 120mmHg then discuss with project team.
4.11	○	○	Has the patient had any blackouts or faints since the last visit? → **If Yes**, then discuss with project team.

5. Medication plan at this visit

	Yes	No	
5.01	○	○	Any changes to antihypertensive treatment? → **If Yes**, update Antihypertensive Medication form (MA)
5.02	○	○	Any changes to other types of medications? → **If Yes**, update Other Medication form (MO)

6. Samples

	Yes	No	N/A	
6.01	○	○	○	Blood forms for visit to diagnostic med lab given?
6.02	○	○		Is this a 6 month visit? → **If Yes**,

	Yes	No	
6.03	○	○	Has a 6 month 24 hour urine been arranged? → **If Yes, please complete 24 hour urine results**

DEFEND
Delay future end stage nephropathy due to diabetes

Form C: Follow-up Assessment
(Intensive Participants)

Participant initials ☐☐

Registration number ☐☐☐-☐☐☐

Affix registration label here

Remember: an extra 24hr urine to be done when BP first reaches target.

6.04 Yes ○ No ○ Is the BP on today's visit <130/80?

→ **If Yes,**

6.05 Yes ○ No ○ N/A (done previously) ○ Has a 24 hour urine been arranged?

→ **If Yes, please complete 24 hour urine results**

24 hour Urine results (when available)

6.06 ☐☐☐☐2☐0☐☐ Date of collection
day month year

6.07 ☐☐☐ 24 hour Urine creatinine
mmol/day

6.08 ☐☐☐☐ Urine volume
mls

6.09 ☐☐☐ 24 hour Urine sodium
mmol/day

6.10 ☐☐☐ 24 hour Urine urea
mmol/day

6.11 ☐☐☐☐☐ Urine protein
mg/day

7. General comments

DEFEND
Delay future end stage nephropathy due to diabetes

Form C: Follow-up Assessment
(Intensive Participants)

Participant initials ⌊⌊⌊⌊

Registration number ⌊⌊ - ⌊⌊⌊

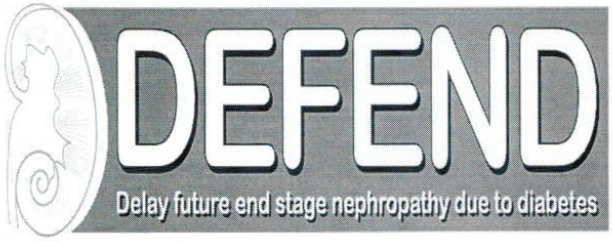
Affix registration label here

8. ⌊⌊:⌊⌊ End time (24 hour)
hh *min*

9. Signature

9.01 _____ _____ ⌊⌊⌊⌊ 2 0 ⌊⌊
signature *printed name* *day* *month* *year*

Appendix B



Patient Education Package

Contents

Being part of the study

We will:

- Give you information on diabetes, kidney function, blood pressure, smoking, healthy eating and exercise.
- Arrange extra blood tests (initially and at 1 & 2 years)
- Do a 24 hour blood pressure check (initially and at 1 & 2 yrs)
- Do a ECG - heart tracing (initially and at 1 & 2 years)
- Perform heart ultrasound study (initially and at 1 & 2 years)
- Aim to work alongside your usual health care giver (Family Doctor, Kidney or Diabetes Specialist) and we will keep these doctors informed of your medication, blood tests and blood pressure.
- Give you petrol vouchers or bus fares to assist with the added costs of your transport to & from these visits where needed

If you are in the intense treatment group, allocated to the Healthcare Assistant, there will be a few additional visits and we will also:

- Monitor your blood pressure monthly with a health care worker visiting you at home, work, marae, church, community, hospital or family doctors practice.
- Change your blood pressure tablets if necessary to control your blood pressure and give you the prescriptions you need for these changes.
- Monitor your blood tests 3 monthly

Pharmacy

1. This project will only manage medications related to your **blood pressure control.**

2. All medications prescribed for you by the hospital, your family doctor or specialist doctors are **IMPORTANT.**

3. **Always** take your yellow medication card with you when you are going to the hospital, to your family doctor, specialist doctors or Accident/Emergency Clinic so they have an up to date list of all of your medications.

4. Tell us when you next meet the nurse/Healthcare Assistant of any medication changes that have been made or added.

5. Tell us of any extra remedies you are taking:
   - Pills/ tonics you buy over the counter or from a pharmacy
   - Treatments you get from the Naturopath, Homeopath, acupuncture, healer etc
   - Pills / tonics you buy from the supermarket/Health food Shop
   - Pills, Tonics or potions friends or family give you

6. There are many benefits of building up a relationship with one pharmacy (usually your local one). You get to know them, they get to know you and the pharmacist can ensure you are getting the appropriate subsidies.

   Ask your pharmacist if there is any way the cost of your medications can be reduced. Some people qualify for a community services card or a high user card.

   Are you paying more than you need on your prescriptions? Please consider the above questions and speak to your local pharmacy.

Blood Pressure

1. What is Blood Pressure?

Blood is carried from the heart to all parts of your body in vessels called arteries. Blood pressure is the force of the blood pushing against the walls of the arteries. Each time the heart beats (about 60-70 times a minute at rest), it pumps out blood into the arteries.

Your blood pressure is at its highest when the heart beats, pumping the blood. This is called systolic pressure. When the heart is at rest, between beats, your blood pressure falls. This is the diastolic pressure. Blood pressure is always given as these two numbers, the systolic and diastolic pressures. Both are important. Usually they are written one above or before the other, such as 120/80. The top number is the systolic and the bottom the diastolic. When the two measurements are written down, the systolic pressure is the first or top number, and the diastolic pressure is the second or bottom number (for example, 120/80). If your blood pressure is 120/80, you say that it is "120 over 80."

A healthy blood pressure level should be lower than 130/80. When the level stays high (>130/80) you have high blood pressure.

2. How can blood pressure harm me?

Unfortunately, high blood pressure acts silently and causes blood vessels in your brain, head and kidneys to be damaged. Unchecked this can cause a stroke, heart attack or kidney failure. This is particularly true in patients with diabetes whose kidneys are already showing damage with protein leaking into the urine and an elevated kidney blood test (Creatinine) such as yourself.

3. Ways of helping to reduce your blood pressure

- Taking your blood pressure pills regularly
- Maintaining a healthy weight
- Following a healthy eating plan which includes; foods lower in salt/sodium
- Stopping smoking
- Being physically active
- Alcohol in moderation

Think of your blood pressure pills as your "kidney protection" pills. Most patients with diabetes and high blood pressure need 3 or more different types of blood pressure pills to bring the pressure down to levels that help the kidneys. This project has been carefully planned to try and give you once a day blood pressure pills and combination pills where possible so as to make it easier for you to take your medication.

4. How does lowering my blood pressure help?

By having healthy blood pressures (less than 130/80) you can help reduce your chances of a stroke and heart attack by large amounts. A major additional benefit is the protection this will give you against on going kidney damage.

5. Are there dangers of taking blood pressure pills?

Blood pressure pills like all other pills can cause side effects in some patients. The pills we have chosen for this study are widely used and have been shown to be very safe and effective. Please discuss any concerns you may have with your doctor or one of the research team.

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Maintaining a Healthy Weight

Aim to maintain your weight within the **healthy weight range**.

Body Mass Index (**BMI**) is a measure of body fat based on height and weight.

Aim for a Body Mass Index of between 20-27 which is within the healthy weight range.

Check with your doctor, nurse or dietitian what your BMI is.

Another simple and useful guide to check whether you are within the healthy weight range or maybe overweight is to measure your **waist circumference**. A measurement is taken around your body at the level of your tummy button.

To be within a healthy weight range **men** should have a waist circumference of **less than 102cm** and **women less than 88cm**.

Eating a Healthy Diet

Following a healthy diet can help reduce high blood pressure.

Choose a healthy meal plan which:

- is lower in salt (sodium)
- is low in saturated (animal) fat and cholesterol
- includes at least 5 serves of fresh fruit and vegetables each day
- is limited in alcohol.

Tips to lower salt (sodium)

- use reduced sodium or no added salt products
- buy fresh, frozen or canned low salt vegetables

- use fresh poultry, fish and lean meat rather than canned, smoked or processed
- use spices or herbs instead of salt in cooking and at the table.

Tips to lower saturated fat and cholesterol

- choose lean meats, poultry and fish
- Trim all fat off meat and remove skin from chicken
- Steam, boil, roast, bake or grill rather than fry
- Limit butter, dripping or lard. Use a little oil in cooking if necessary.
- Choose low fat foods such as low dairy products, lite coconut milk, low fat meats
- Choose foods with the Heart Foundation Tick √

How to include more fruit and vegetables

- Eat fruit as a snack instead of biscuits or bread
- Serve more salads and vegetables on your dinner plate and reduce the amount of meats
- Add fruit to cereal at breakfast, with yoghurt at lunch or as a dessert after dinner
- Fill your sandwiches with greens and use less meat, cheese and other filling.

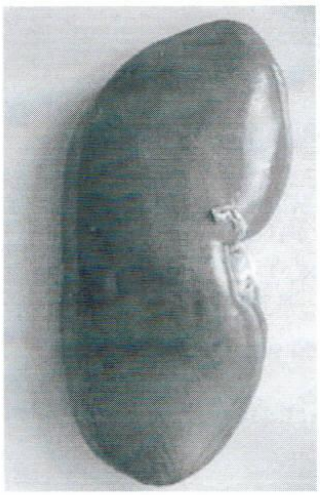
What about alcohol

- A small amount of alcohol may provide health benefits.
- Some people should not drink alcohol so ask your doctor or nurse. Limit alcohol to 2 drinks per day for women and 3 drinks for men.

The Kidneys

What do your kidneys do?

Your kidneys are organs with filters that remove waste from the blood. This waste is then passed out of the body as urine.



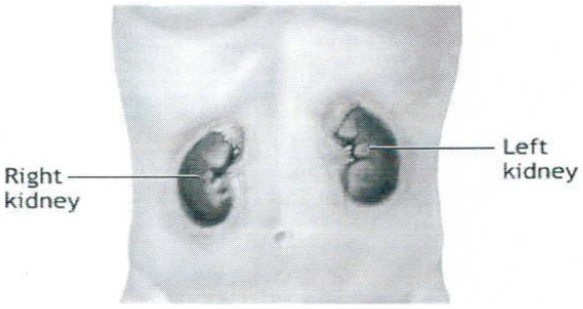
Blood is pumped to the kidneys, where there are hundreds of thousands of tiny blood filters. Blood cells, protein and anything else that is needed, stay in the blood. Urine flows to the bladder so it can then be passed out of the body

When the kidneys are affected by diabetes, or high blood pressure the blood filters become damaged. Whilst blood is pumped to the kidneys normally, the weakened filters don't do their job properly and "**leak**" some of the **protein** into the **urine.**

This is why your **doctor measures the amount of protein in the urine to see if you have any kidney damage.**

If the damage continues, the kidneys lose their ability to cleanse the blood. Without treatment, the kidneys will become increasingly damaged & not be able to do their job properly.

When there is a lot of damage you may need dialysis or a transplant to make up for the loss of normal healthy functioning kidneys.



How to take care of your kidneys?

- Blood pressure control usually with medication (kidney pills)
- Stop smoking
- A healthy diet
- Good blood glucose control

In many cases this can slow the progression of kidney damage.

Diabetes

1. What is Diabetes?

Diabetes is diagnosed when the blood glucose (sugar) is higher than it normally should be. Many people with diabetes are unaware they have the condition. However, some people have symptoms including thirst, passing large volumes of urine and weight loss.

2. How does diabetes affect you?

Many people with diabetes are unaware they have the disease. However when the blood glucose (sugar) remains high it causes damage to small blood vessels in the eyes and kidneys and can affect the feeling in the feet.

When the damage to the kidneys is at an advanced stage the kidneys can fail to work altogether.

A high blood glucose (sugar) also increases the chance of a stroke, heart attack and the possibility of having an amputation.

3. What treatments are available?

A healthy diet and active lifestyle are the most important parts of any program to control blood glucose (sugar). If the blood glucose (sugar) remains elevated despite these lifestyle measures then medication can be used. In some instances taking these medications will not make you feel any better but will lower the chance that the complications of kidney and heart disease will develop. If tablets are not sufficient to lower the blood glucose then insulin treatment may be used.

4. What can I do to help?

Eating a healthy diet and exercising regularly are very important measures to lower the risk associated with diabetes. You can also check your own blood glucose (sugar) with a finger prick device and a machine that reads your blood glucose (sugar). In general, readings before a meal should be somewhere between 4 – 7 mmol/L and 2 hours after a meal around less than 8 mmol/L.You can also be checked out by your general practitioner through the Get Checked Program.

Smoking

1. What types of smoking are there?

Cigarettes, roll your own cigarettes, pipe smoking and cigar smoking as well as exposure to the smoke from other people smoking (passive smoking) are all forms of smoking.

2. What are the effects of smoking?

Smoking has many serious effects on the body especially after smoking for many years. Smoking damages blood vessels, which can lead to heart attacks and strokes. Cigarette smoke also damages the lungs and this can lead to severe breathing difficulties. In addition, cigarette smoking is the most important cause of lung cancer. Men should be aware that smoking increases the risk of developing impotence.

3. How can I stop smoking?

Please contact the Quitline 0800 778 7778 who will provide you with advice on what steps to take to stop smoking.

4. Is it worth stopping smoking?

YES! It is certainly worth stopping smoking. No further lung damage occurs when the smoking is discontinued. The risk of having a heart attack or stroke also diminishes over time. It's never too late to stop smoking and the longer it is since you have stopped smoking the greater the benefits you will experience.

Exercise

1. Why is exercise good for you?

Exercise helps to reduce weight. Even a small amount of weight loss of around 5kgs will reduce blood pressure, lower blood glucose (sugar) and reduce the risk of heart disease. Exercise also helps you to feel better within yourself and feel more motivated.

2. What sort of exercise?

The best sort of exercise is exercise that you enjoy and that is safe for you to do. There are many different types of exercises which you can consider. However, brisk walking is probably one of the best forms of exercise.

3. For how long should I exercise?

If you have not exercised before than you will need to start slowly perhaps with just a few minutes a day. The goal is for you to gradually increase the amount of exercise you are doing so that each day you are exercising for about 20 minutes.

4. Is it safe for me to exercise?

If you have not been exercising up until now it would be wise to meet with your family doctor to ensure that it is safe for you to exercise. If while you are exercising you experience chest pain or tightness or excessive breathlessness you should see you doctor promptly.

References: 1) Auckland Diabetes Nurse Specialist Group (2004) Diabetes Resource manual: Education Beats diabetes 2) Kidney Care, How well are your kidneys? 3) National Heart Foundation (2000) Healthy Heart Quiz 4) National Heart Foundation (2003) What is Cholesterol? 5) Website: Pictures & images: http://health.allrefer.com/