Original Article:

Long-term effectiveness of a community-based model of care in Māori and Pacific patients with type 2 diabetes and chronic kidney disease: A 4-year follow-up of the DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study

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Short title:

Follow-up of the DEFEND trial

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Abstract

Background: The DEFEND study was a randomized controlled trial of Māori and Pacific patients with advanced diabetic nephropathy, comparing a community-based model of care with usual care. The intervention group achieved lower BP, proteinuria and less end-organ damage [1]. After the intervention ended, all patients reverted to usual care, and were followed to review the sustainability of the intervention.

Design: A retrospective observation of 65 patients (aged 47–75 years) with type 2 diabetes, hypertension, CKD 3/4 and proteinuria (>0.5 g/day) previously randomised to intervention/community care or usual care for 11-21 months. Follow-up thereafter was until death, ESRD (eGFR ≤ 10ml/min/1.73m^2)/dialysis or 1st February 2014.

Primary endpoints were death and ESRD/dialysis. Secondary outcomes were annualised GFR decline, non-fatal vascular events and hospitalizations.

Results: Median (IQR) post-trial follow-up was 49 (21-81) months and similar in both groups. The median (IQR) eGFR decline was -3.1 (-5.5, -2.3) and -5.5 (-7.1, -3.0) ml/min/year in the intervention and usual care groups respectively (p=0.11). Similar number of deaths, renal and vascular events were observed in both groups.

At the end of follow-up, the number of prescribed antihypertensive medications was similar (3.4 ± 1.0 vs. 3.3 ± 1.4; p=0.78). There were fewer median (IQR) hospital days [8 (3, 18) vs. 15.5 (6, 49) days, p=0.03] in the intervention group.

Conclusions: Short-term intensive BP control followed by usual care, did not translate into reduction in long-term mortality or ESRD rates, but associated with reduced hospitalisations.

Introduction

In New Zealand, diabetic kidney disease is the most common cause of end stage renal disease (ESRD) requiring renal replacement therapy (RRT). It is particularly prevalent in Māori and Pacific people [2], with a 12-14 fold increased incidence of ESRD compared to non-Māori [3]. Furthermore, patients with diabetes have a greater risk of cardiovascular mortality compared to non-diabetic patients [4], with an excess risk in those with renal dysfunction [5].

Progression to ESRD is strongly associated with proteinuria and hypertension. These are characteristics commonly found in Māori and Pacific patients with diabetic nephropathy, who have a faster rate of glomerular filtration rate (GFR) decline and are more likely to develop ESRD than other ethnic groups in New Zealand [6]. This increased risk is attributed to a higher prevalence of obesity, poorer glycated haemoglobin (HbA_{1c}), higher smoking rates in Māori, family history of renal disease, higher levels of albuminuria [7, 8], and earlier onset of type 2 diabetes [3].

Poorer health outcomes in Māori and Pacific patients may be associated with a high proportion of unmet need for primary health care due to transport and cost limitations, and inability to get appointments with their usual primary care physicians in a timely fashion [9]. Previous community-based interventions have shown promising results when compared to conventional approaches in the management of chronic diseases. Hill et al. [10] demonstrated a beneficial effect on blood pressure (BP) control, surrogate cardiac and renal markers in disadvantaged African American men following a 3-year intervention. However, no long-term outcomes have been reported. Similarly, cultural considerations in implementing health care interventions in Māori and Pacific patients which involved family or community groups were more likely to succeed with improved patient involvement and adherence [11].

Proteinuria is an important predictor of ESRD and attaining remission of this has been observed to substantially reduce the development of ESRD and improve life expectancy in patients with diabetes and overt proteinuria [12, 13]. Patients with type 2 diabetes have a high prevalence of left ventricular hypertrophy (LVH) which heightens their risk of premature cardiac mortality and may be reduced with normalization or regression of LVH, associated with BP and weight reduction [14].

The DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study was a 12-month randomised controlled trial (RCT) which tested a novel community approach to try and overcome some of these recognised barriers to care that lead to poor health outcomes in Māori and Pacific people [1]. Sixty-five Māori and Pacific patients, with uncontrolled hypertension and stage 3 or 4 chronic kidney disease (CKD) secondary to diabetic nephropathy, were randomly assigned either to a community-based intervention (n=33) or usual care (UC) (n=32). The intervention group received monthly home visits from ethnic-concordant health care assistants who were supervised by a nurse coordinator to optimise BP. Both groups continued to receive care by primary health care providers, and secondary care specialist diabetes and renal clinics [1].

At the start of the study, all patients received comprehensive education and advice on regular exercise, smoking cessation, reduced dietary salt intake, and the importance of optimal BP control and medication adherence. At 12 months, the intervention group achieved a significantly lower BP compared to patients managed solely by usual care (140/78 vs 149/77mmHg, $p<0.05$). This short-term community intervention resulted in a reduction in 24-hour urinary protein excretion from baseline (-1.4 ± 2.6 g vs +0.1 ± 2.8 g, $p=0.04$), and statistically significant echocardiographic changes from baseline. The mean LV mass of patients in the intervention group remained unchanged compared to an increased mean LV mass in the

UC group at 12 months – two important determinants of renal and cardiovascular outcomes. Following the completion of the intervention, all patients reverted to usual care only.

The aim of this follow-up post-trial study was to compare the longer-term outcomes between the intervention and UC groups so as establish whether the effect of the short-term community intervention would translate into measurable longer term benefits despite return to usual care.

Materials and methods

The DEFEND trial was conducted at the University of Auckland, Department of Medicine. The details of the study's design and methods have been previously published [1]. The original study was planned as a 2-year intervention but due to slow recruitment, was curtailed and outcomes for patients following the first 12 months of intervention were reported in the DEFEND study. Some patients had however been in the intervention study for up to 21 months (median 17 months, range 11-21 months).

We report on the outcomes after the intervention was completed and when all patients had reverted to usual care. Ethics approval was obtained from both the local ethics committee, and Māori and Pacific Island Health Services in the community and hospital. Patients had previously provided written informed consent.

Data source and patients

Three patients in the intervention group had reached study endpoints during the 12 months of the initial study. One patient was commenced on dialysis within 7 months of recruitment, one

died of cancer at 6 months, and another had a cardiac arrest at 10 months. We conducted a retrospective follow-up study of the remaining 62 patients from the DEFEND cohort.

Each patient had a unique hospital identifier which was linked to their hospital and clinic records, dispensed prescriptions and mortality data. Using these hospital records, we recorded clinic HbA_{1c}, retinopathy and smoking status, serum creatinine, estimated GFR (eGFR) and prescribed antihypertensive medications. We measured eGFR using the 4 component Modification of Diet in Renal disease (MDRD) equation [15] and recorded HbA_{1c} measurements only when corresponding haemoglobin levels were >100 g/L to correct for renal anaemia in patients with CKD. Patients were followed up until a renal event (a composite outcome of ESRD defined as eGFR ≤10ml/min/1.73m^2 or RRT), death or 1st February 2014.

Study outcomes

The primary endpoints were all-cause mortality or a composite renal event (ESRD or RRT). Secondary outcomes included annualised eGFR decline (defined as the difference between eGFR at recruitment to the DEFEND study and at the end of follow-up, divided by the duration of follow-up), inpatient hospital days and a composite endpoint of macrovascular complications prior to ESRD. The latter consisted of cardiovascular events (non-fatal myocardial infarction, heart failure, coronary artery bypass graft and percutaneous coronary angioplasty); cerebrovascular events (ischaemic strokes and transient ischemic attacks) and peripheral vascular disease (angioplasty, bypass and amputation). Patients were censored when they had reached the composite endpoint of RRT/ESRD, death, or when lost to follow up.

Statistical analysis

Statistical analysis was performed using STATA software (version 13.1). Continuous variables are expressed as mean (± SD) and were compared using Student's t-tests or analysis of variance (ANOVA) as appropriate. Medians are presented with interquartile ranges (IQR) and compared using Mann-Whitney test. Categorical variables are expressed as proportions and were compared using the X^2 test. P <0.05 was considered significant and all tests were two-tailed. Kaplan-Meier cumulative estimates were conducted to compare the primary endpoints of death and renal event between the 2 groups, censoring for loss of follow up or the end of this post-trial study.

Results

The median length of intervention during the RCT was 17 months (range 11 – 21 months) with subsequent median post-trial follow-up of 48 (IQR 20 – 83) and 52 months (IQR 25 – 68) in the intervention and UC groups respectively (*p*=0.98). Characteristics of the patients at recruitment, at 12 months of the study, and at the end of follow-up are shown in **Table 1**. No significant intergroup differences were observed for HbA_{1c}, haemoglobin level, eGFR, smoking and retinopathy status at the end of the post-trial follow-up. At the end of the follow-up, the proportion of patients with a smoking history and retinopathy status were similar to that at baseline.

Primary outcomes

Four years following the DEFEND study and cessation of intervention, the event rate for the composite outcome of all-cause mortality or renal events was high, affecting 46 (74%) patients in this cohort and was similar in both groups **(Table 2)**. Six patients in the intervention group

had died – 4 of malignancy, 1 cardiac and 1 unknown. Ten patients in the UC group had died – 4 related to ESRD, 1 malignancy, 1 cardiac, 1 multi-organ failure, 1 sepsis and 2 from unknown causes, with a trend towards an increased ESRD-related mortality in the UC group (p=0.045).

A similar proportion of patients from both groups were established on dialysis or reached ESRD. Fifteen of 30 (50%) patients from the intervention group, and 15 of 32 (47%) patients from the UC group (p=0.81). The median rate of annualised eGFR decline from baseline was similar in the in both groups (-3.1 (-5.5, -2.3) vs. -5.5 (-7.1, -3.0) ml/min/year) **(Table 2)**. There was no survival or renal advantage demonstrated for patients who received community-based intervention over usual care during follow up from the time of recruitment **(Figure 1)**.

Patients in the intervention group were divided into 3 groups according to the duration of the intervention received. Ten patients received 11–16 months, 12 patients 17 months and 8 patients 18–21 months of intervention. There was no significant difference observed for outcomes of all-cause mortality (p=0.90) or renal events (p=0.067) between both groups.

Secondary outcomes

A total of 33 macrovascular complications occurred, affecting 28 patients (11 from the intervention group and 17 patients from the UC group). These were predominantly cardiovascular events and occurred equally in both groups (p=0.13). Two patients in the intervention group and 3 in the UC group suffered from 2 separate vascular events respectively.

There were fewer inpatient hospital days in the intervention group (median (IQR) 8 (3–18) vs. 16(6–49) days; p<0.05) compared to that observed in the UC group during the post-trial follow-up **(Table 2)**. The number of antihypertensive medications prescribed in both groups was

comparable at the end of the study (p=0.71) **(Table 1)**, with similar proportion of patients in both groups on either angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) (97% vs. 88%, p=0.19) and diuretics (63% vs. 66%, p=0.85).

Discussion

In this 4 year post-trial follow-up of the DEFEND study, we evaluated the longer term impact of intensive BP control over 11–21 months in patients with type 2 diabetes and CKD 3/4, delivered through an integrated, community-based model compared with usual care.

Although patients in the intervention group achieved lower BP, less proteinuria and no progression of LV hypertrophy at 12 months when compared to those in the UC group, this did not translate into sustained and improved clinically meaningful outcomes after reverting to routine care.

In our study, 74% of patients reached the endpoints of mortality or ESRD/RRT with no survival or renal difference between both groups. Although less than 20% of patients had documented pre-existing cardiac disease at baseline, 32% of patients had suffered a cardiovascular event by the end of our follow-up, with a non-significant 28% relative reduction in event risk for patients who had received the intervention. The proportion of cardiovascular events in the DEFEND cohort [1], particularly in the intervention group, was similar to that seen in the RENAAL study which affected 33% of patients [16].

The high renal event rate was unsurprising as high levels of albuminuria and lower GFR are independent and synergistic predictors of progression of renal disease [17]. The mean rate of GFR decline in this population appears to be comparable to that observed in a similar cohort with type 2 diabetes and macroalbuminuric CKD 2, but who had higher renal reserve at

baseline [12]. In that study, an annual eGFR decline of 5.2 ml/min/1.73m^2 was reported, with only 54% of patients on an ACEi or ARB. When compared to a subgroup of patients from the DIAMETRIC database [4] with similar baseline eGFR, renal events occurred at a higher rate in our study.

Overall, we found a 26% mortality rate over the 4.8-year follow-up which is similar to the annualised total mortality of 4.6% observed in the follow-up study from the DIAMETRIC database where only 25% of their patients had macroalbuminuria and eGFR ≤ 45 ml/min/1.73m^2 [4]. On the contrary the ADVANCE cohort [18] showed a statistically significant but perhaps a less clinically meaningful 9% reduction in mortality in patients who had received BP lowering intervention.

The poorer renal outcomes in our study were likely related to the advanced CKD stages at the time of recruitment. The improved management of cardiovascular diseases in patients with type 2 diabetes in recent years has also increased patient survival long enough to reach ESRD such that it now exceeds fatal cardiovascular events to become a common outcome in those with advanced diabetic nephropathy [4]. Furthermore, Māori and Pacific people have additional metabolic risk factors associated with poorer renal prognosis [7, 19]. Severe retinopathy, a marker of microvascular damage, was also present in more than half of our patients. Diabetic retinopathy, together with high levels of proteinuria, is associated with higher rates of ESRD and mortality [13, 20].

The number of prescribed anti-hypertensive medications between both groups was similar at the completion of the post-trial follow up. It would appear that in the period after the trial, both primary and secondary care clinicians have taken a more active approach in achieving BP targets. While this may partly be a consequence of their patients' involvement in the DEFEND trial, it more likely relates to an increase in the overall awareness of the importance of BP

control. As a result, this may have minimized the difference in study outcomes between the intervention and UC groups upon return to routine care.

We found fewer inpatient days in the intervention group associated with fewer hospitalizations during the post-trial follow-up. The significance of this finding is unclear and it did not lead to any survival or renal advantage. It is conceivable that the more intensive education provided to the intervention group resulted in improved health literacy, leading to better overall personal care and timely access to primary healthcare. Based on this finding, implementation of community-based interventions could lead to greater healthcare savings. Community-based programmes are integral to the management of chronic illness. A systematic review of 15 studies involving home visiting programmes (of varying duration and intensity) in older people showed that such interventions were effective in reducing mortality and admissions into permanent institutional care, and possibly fewer hospitalisations although the latter was not statistically significant [21]. Further research is still required to establish an optimal duration and intensity of community-based interventions in delivering effective and efficient health care to high-risk groups.

There are several limitations to this study. Firstly, the small sample size limits interpretable significance of associated treatment effects. However more than 50% of patients in the DEFEND study had reached ESRD by the end of the post-trial follow-up, confirming the poor prognosis normally associated with diabetes and CKD. Secondly, the lack of systematic post-trial BP and urine PCR measurements prevents correlation of these clinical parameters to outcomes. However this study was aimed at reviewing concrete and meaningful outcomes which could emerge from a short-term trial of intensive BP control. Thirdly, it is not possible to assess medication adherence during the follow-up phase which would affect the success of the intervention.

Current efforts are targeted towards identification and prediction of CKD progression [17] which needs to be matched by a systematic, effective and economical management process to retard the progression towards ESRD. The cardiovascular and renal benefits seen at 12 months in the DEFEND cohort did not translate into longer term improved clinical outcomes and highlights the management difficulties faced with these high-risk patients in clinical practice. To achieve improved outcomes, intensive community-based interventions may need to be commenced earlier and maintained longer term. However the costs and benefits of such a strategy would need to be explored before wider adoption of this approach can be recommended.

Acknowledgments

This is a follow-up study of the DEFEND trial which was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN1260500012662).

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Figure 1a. Kaplan Meier cumulative survival estimates of Community (n=33) and Usual care (n=32) groups from recruitment, adjusted for HbA1c, eGFR and presence of diabetic retinopathy (*p*=0.53).

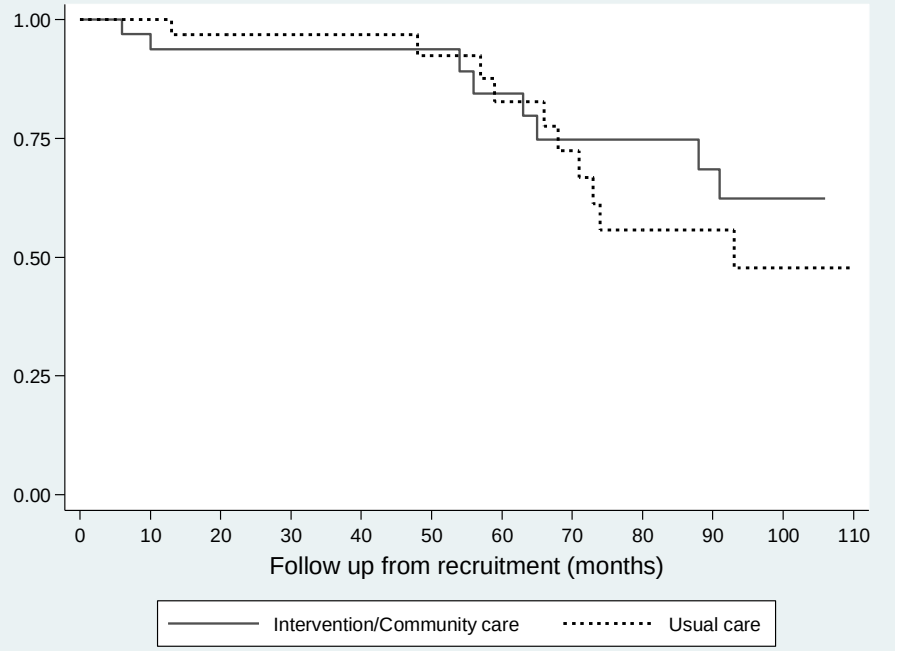

Figure 1b. Kaplan Meier cumulative renal survival estimates of Community (n=33) and Usual care (n=32) groups from recruitment, adjusted for HbA1c, eGFR and presence of diabetic retinopathy (*p*=0.80).

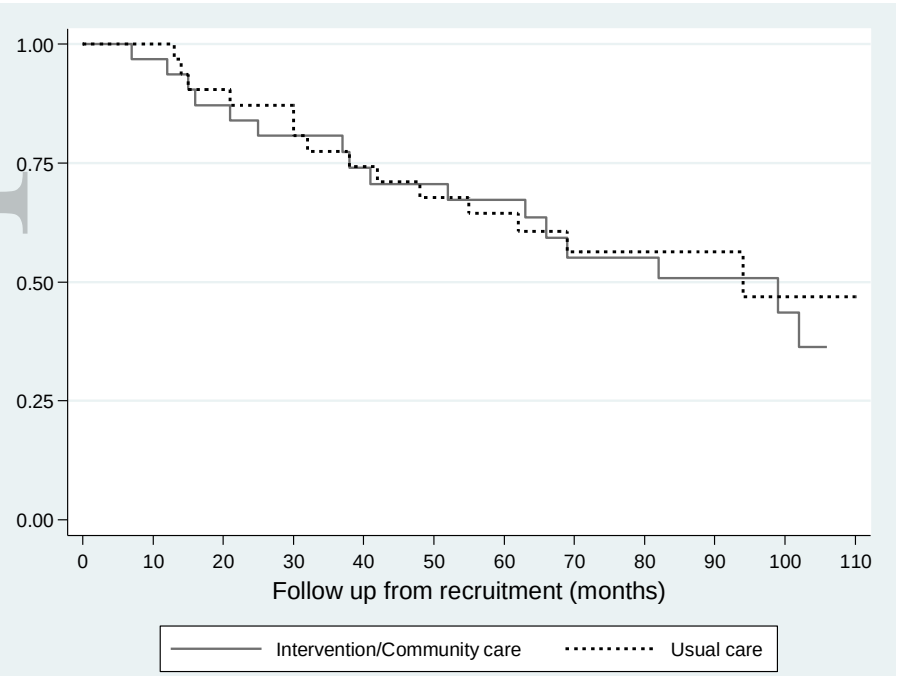

Table 1. Comparison of HbA_{1c}, eGFR and number of antihypertensive agents between the intervention and usual care group at baseline, 12 months and at the end of follow-up after the completion of intervention, and when all patients had reverted to usual care. Baseline and 12 months characteristics have been previously reported in the DEFEND study [1]. Four patients in the Usual Care group who had initially been lost to follow up at 12 months had available medical records and are reported in this follow-up study.

Findings are expressed as mean ± SD unless otherwise stated.

HbA_{1c}: Glycated haemoglobin; eGFR: estimated glomerular filtration rate (4-point MDRD calculation) [15]

	Intervention Group			**Usual Care Group**		
	Baseline (n=33)	12 months (n=30)	Post-trial follow up (n=30)	Baseline (n=32)	12 months (n=28)	Post-trial follow up (n=32)
Follow up, months (IQR)			47.5 (20.25, 82.5)			52 (24.5, 68)
HbA_{1c} (%)	8.3 ± 1.6	8.0 ± 1.9	7.7 ± 1.4	8.5 ± 1.9	7.9 ± 1.7	7.4 ± 1.2
mmol/mol	67 ± 17	63 ± 20	61 ± 15	69 ± 20	62 ± 18	57 ± 14
eGFR, ml/min/1.73m^2	36 ± 15	33 ± 17	18 ± 16	39 ± 14	41 ± 18	18 ± 16
No. of antihypertensive agents, n	2.2 ± 1.3	3.4 ± 1.1*	3.4 ± 1.0	1.9 ± 0.9	2.3 ± 1.0	3.3 ± 1.4

*p<0.05 (Intervention vs. usual care group at 12 months)

Table 2. Comparison of clinical outcomes between the Intervention and Usual Care groups at the end of post-trial follow-up.

ESRD: End stage renal disease; eGFR: estimated glomerular filtration rate; RRT: renal replacement therapy

† Primary composite endpoint: all-cause mortality or renal events (composite of ESRD defined as <10ml/min/1.73m^2 and/or RRT)

‡ Secondary composite endpoint = non-fatal and fatal cardiovascular, cerebrovascular or peripheral vascular disease.

Outcome	**Intervention (n=30)**	**Usual care (n=32)**	***p-value***	**Relative risk (95% CI)**
Primary composite endpoints†				
No. of patients (%)	6 (20%)	10 (31%)	0.31	
All-cause mortality	0 (0%)	4 (12.5%)	0.045	0.65 (0.3 – 1.5)
Renal deaths	1 (3%)	1 (3%)	0.96	
CVD deaths				
	15 (50%)	15 (47%)	0.81	1.1 (0.6 – 1.8)
Renal events				
Secondary composite endpoint ‡				
No. of patients (%)	11 (37%)	17 (53%)	0.12	0.7 (0.4 – 1.2)
Total no. of macrovascular complications	13 (43%)	20 (62.5%)	0.13	0.7 (0.4 – 1.1)
CVD	8 (27%)	12 (37.5%)	0.36	0.7 (0.3 – 1.5)
CVA	2 (7%)	2 (6%)	0.95	1.1 (0.2 – 7.1)
PVD	3 (10%)	6 (19%)	0.33	0.53 (0.2 – 1.9)
Annualised eGFR decline; ml/min/1.73m^2/year				
median (IQ Range)				
Baseline-12 months	-1.8 (-6.9,1.8)	0.3 (-5.7,6.7)	0.15	
Baseline-end of study	-3.1 (-5.5, -2.3)	-5.5 (-7.1, -3.0)	0.11	
Inpatient Hospital days				
Median (IQ Range)	8 (3, 18)	15.5 (6, 49)	0.025	