

Effects of Multi-factorial Intervention Models on Cardiovascular and Renal Outcomes in Patients with Type II Diabetes

A Pharmacy Practice Paper

NOTE: The appendix for this paper is not included in the example, but was included in the final paper submission.

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INTRODUCTION

It wasn't long ago that "maturity onset diabetes" or type II diabetes was thought to be a relatively benign disorder with a modest impact on life expectancy¹. Now we know that life expectancy for over 2 million Canadians with type II diabetes mellitus is shortened by 5-10 years.² The leading cause of death in this population is heart disease and stroke which account for approximately 65% of deaths.³ Cardiovascular morbidity and mortality in patients with diabetes is 3 to 20 times higher than in the general population at similar age⁴. Mortality associated with diabetes complications is approximately 41 500 Canadians per year.²

In addition to an increased risk of cardiovascular morbidity and mortality, type II diabetes represents the cause of 33% of end stage kidney disease (2002). This is a 22% increase from 1990 and a number that is expected to continue to rise.⁵ The risk of diabetic microalbuminuria or worsening nephropathy in type II diabetes is modeled to be approximately 28% after 15 years.⁶ The number of new patients starting dialysis each year in Canada (2002) is 4961. This number has doubled in the last decade.⁷ According to Canadian statistics, between 1991-2000, 70% of patients die within 10 years of starting dialysis. Patients with diabetes and cardiovascular disease upon starting dialysis are twice as likely to die within this time frame.⁸

The overall incidence of diabetes in Canada and world-wide is on the rise and is expected to double by 2025.⁹ In Canada driving forces for this epidemic are an aging population, increasing obesity, sedentary lifestyles, large aboriginal population, and a growing incidence of type II diabetes in children. In addition, 77% of new Canadians come from populations that are at higher risk for type II diabetes (Hispanic, Asian, South Asian, or African descent). Costs to the Canadian health-care system from diabetes and its complications are estimated at 13.2 billion/year and are estimated to increase to 19.2 billion by 2020.²

Clearly these statistics demonstrate a need for interventions that can reduce the risk of morbidity and mortality associated with type II diabetes and its complications, particularly those of cardiovascular and kidney disease. While, many interventions have been shown to impact the natural progression of disease, no single intervention has been able to eliminate the risk of cardiovascular and renal complications in this population.

Reducing Risk Factors for Cardiovascular Disease and Kidney Disease Progression in Type II Diabetes

During the last decade, conclusive evidence has been gathered that modifying risk factors is of immense importance in the prevention of cardiovascular and renal complications in type II diabetes.¹⁰ Several single risk factor targeted trials

have demonstrated the efficacy of the treatment of hyperglycemia¹¹, hypertension¹²⁻²³, elevated levels of serum cholesterol²⁴⁻³⁰, an increased albumin excretion^{31,32}, and smoking³³ in reducing a variety of cardiovascular events and vasculopathies.^{31,34}

Not surprisingly, the risk factors for the progression of chronic kidney disease (CKD) are not greatly different from those that increase cardiac risk and include age, ethnicity, hypertension, microalbuminuria, dyslipidemia, poor glucose control, smoking, and anemia.³⁵ Intervention studies have likewise demonstrated benefits in renal outcomes through modification of several of these risk factors including: hypertension³⁶, glucose control³⁷ and albuminuria.^{34,38,39}

Therefore, the path towards better cardiovascular health for people with type II diabetes runs parallel to the course of action needed to prevent the progression of CKD. This paradigm has been recognized by the nephrology community and has changed the approach to the patient with diabetes and CKD.⁴⁰

Implementation of Known Risk Reduction Interventions By The General Practitioner (GP)

Despite a plethora of evidence surrounding the benefits of meeting predefined targets of A1C, blood pressure, lipid profile, urinary albumin excretion, smoking status, and exercise quota set out by readily available guidelines, the management of these patients is difficult for the GP.

A recent review of administrative records from 12 106 patients of Saskatchewan Health were used to evaluate the use of known interventions in people with type II diabetes and symptomatic atherosclerosis.⁴¹ Fewer than 25% received an antiplatelet agent or an HMG-CoA reductase inhibitor and fewer than 50% received an angiotensin converting enzyme inhibitor (ACEI). Reviews in other countries have demonstrated similar results demonstrating that the family or general practitioner struggles to optimally manage the patient with diabetes and therefore the benefits of these interventions are not being realized.⁴²⁻⁴⁴

Likewise, referrals to nephrologists for renal complications are often late, and interventions that are known to slow progression are often not applied. By the time patients are seen by a nephrologist it is often too late to affect the course of disease.

A review of patients presenting to a nephrologist's office for the first time at a Nephrology centre in Halifax, Nova Scotia was published.⁴⁵ Four hundred and eleven patient charts were reviewed. Seventy-four percent of patients were referred from GPs. Mean serum creatinine at first visit was 274 umol/L (range of 106-981 umol/L). Eighteen percent of patients had a creatinine clearance of less than 18 mL/min. Mean blood pressure was 150/80 and only 44% of patients were on an ACEI or an angiotensin receptor blocker (ARB). Only 60% of diabetics

were receiving one of these agents. Significant anemia (Hgb < 100g/L) was present in 21% of patients and only 35% of patients had an initial work-up for anemia. Metabolic acidosis was present in 25% of patients. Nephrotoxic drugs were recorded; the most common reported agent was an NSAID in 10% of patients. The mean A1C level was 7.9%. Optimal control (A1C \leq to 7.0%) was present in only 24% of diabetic patients. This review clearly demonstrated that pre-referral renal care is not optimized and that referrals to nephrologists are occurring after patients have already developed substantial renal disease and complications.

Early referral to nephrologists for type II diabetic patients has been identified as crucial not only for slowing the progression of renal disease but also for improving survival and reducing morbidity on renal replacement therapy.⁴⁶ Early referral may also be associated with a decrease in overall costs when the starting of dialysis can be deferred or prevented altogether.

In a health care era where the care for patients with diabetes has been shifted from the specialists to the general practitioner (GP), innovative approaches are needed to ameliorate the care of the patient with diabetes. GPs, often required to manage thousands of patients with a multitude of problems, are set up to fail at optimal disease management. A Cochrane review of systems for routine surveillance for people with diabetes mellitus found that disease management strategies with less well-developed support for family doctors were associated with adverse outcomes for patients.⁴⁷ The authors concluded that unstructured care in the community is associated with poorer follow up, greater mortality and worse glycaemic control than hospital care, however some interventions such as computerized central recall with prompting for patients and their family doctors, can achieve standards of care as good as or better than hospital-based outpatient care. Therefore, rather than focusing on single medical interventions that improve care, perhaps the delivery model of that care is as important, if not most important in the optimal delivery of care to patients with type II diabetes.

The purpose of this paper is to review multi-factorial intervention models of care that have demonstrated efficacy in preventing or delaying cardiovascular and renal events in patients with type II diabetes and to describe a multi-disciplinary model for practice in New Brunswick.

EVALUATION OF STUDIES: MULTI-FACTORIAL MODELS OF CARE

A review of the literature identified a large number of evaluations looking at possible models for successful care, of which five are included in this discussion. These 5 studies were chosen because they have a randomised design and have an endpoint of cardiovascular events +/- renal outcomes. These studies are summarized in detail in Table 1.

The Diabetic Intervention Study⁴⁸ demonstrated that a multi-factorial approach can help in the reduction of risk factors and improve smoking cessation, glucose control, blood pressure control, physical activity and reduce alcohol intake. Investigators enrolled patients from 1977-1980, even before it was known that type II diabetes could cause significant morbidity and mortality. However this study was unable to show that an intensified, multi-factorial health education program involving weight reduction, lipid-lowering diets, physical activity, anti-smoking education, blood pressure target < 140/90, and clofibric acid (2-years) reduced cardiovascular events in this population over a 5 year period. Reasons for the failure of this trial to show a benefit may include: inability to lower serum lipid levels with prescribed therapy, higher blood pressure targets and higher blood glucose targets than advocated for today, as well as the absence of specific modern therapeutic agents proven to have a benefit in this population such as HMG–CoA reductase inhibitor therapy and renin-angiotensin system inhibitors.

The Steno-2 trial⁴⁹ demonstrated, with modern interventions, that an intensive multi-factorial intervention strategy can influence hard outcomes. A multi-factorial approach with behavioral modification and stepwise introduction of pharmacological therapy from a hospital based multidisciplinary team (nurse, dietitian, endocrinologist) reduced a composite endpoint of cardiovascular events and death over a 7.8 year period (NNT=5) compared to conventional treatment by general practitioner. The investigators enrolled 160 patients age 40-65 years with type II diabetes and microalbuminuria. They also demonstrated a significant reduction in the development of diabetic nephropathy, retinopathy and the progression of autonomic neuropathy.

Joss et al.⁵⁰ similarly compared intensive treatment involving a hospital based multidisciplinary team (doctor, nurse, and dietitian) that saw patients as often as required to meet multi-factorial targets, compared to routine practice in patients with established diabetic nephropathy. Ninety patients were included in this study. Although targets were the same in each group, the intensive treatment group had better SBP, DBP, and cholesterol. The investigators demonstrated a significant difference in their primary endpoint of reduction in glomerular filtration rate (GFR) decline over two years. They also demonstrated that patients in the treatment group had significantly less hospitalizations and significantly less new cardiovascular events.

Olivarius et al.⁵¹ demonstrated that it does not require a hospital-based clinic of experts to affect outcomes and that it can be done in the general practitioner's office. This research team compared routine care to a structured care model involving general practitioners who were supported by pre-defined follow-up dates with patients, prompting by investigators, access to multi-factorial clinical guidelines, regular feedback and continuing medical education on diabetic care. These investigators, although unable to demonstrate a difference in pre-defined primary outcomes including: overall mortality, retinopathy, MI and stroke, did

show a significant difference in the amount of urinary albumin excretion between the groups at the end of the study period. They also demonstrated improved fasting glucose, A1C, lower SBP, lower cholesterol, additional weight loss, better follow-up, and fewer referrals to diabetic clinics.

Rachmani et al.⁵² demonstrated that patient involvement was an important element of the multidisciplinary team. This team evaluated 165 patients with type II diabetes, hypertension and hyperlipidaemia randomised to either a patient participation and teaching program or standard consultation in a hospital-based diabetes clinic. The patients in the control group were given education regarding multi-factorial modifiable risk factors, records of their consultations and laboratory results. They were encouraged to share these with their primary care giver and request that therapy be intensified if targets were not met. These investigators demonstrated that modifiable risk parameters could be improved in the treatment group. GFR decline was lowered, overt nephropathy was significantly less, and incidence of retinopathy was reduced. All cardiovascular events were significantly reduced in the treatment group.

SUMMARY OF FINDINGS

From these studies, although the practice models vary, it is clear that a structured, multi-factorial approach to the management of patients with type II diabetes significantly improves modifiable risk factors and clinical outcomes such as cardiovascular events and progression of kidney disease. Key components of such treatment appear to be a “therapeutic package” including lifestyle modification, hypertension management, lipid management, glycaemic management, anti-platelet therapy and smoking cessation. Given the multi-factorial complexity of this therapeutic package, it seems intuitive that this therapeutic package be delivered by a multidisciplinary team. Overall, it appears that emphasizing structure and continuous progression towards meeting multi-factorial goals may be more important than actually reaching those goals. In the Steno-2 trial, even in the intervention group, only 15% of patients reached their A1C < 6% target; approximately 70% of patients reached their cholesterol goals, under 50% reached the SBP goal of < 130, and approximately 75% reached the DBP goal of < 80. Despite this, patients in the intervention group did significantly better.¹⁰

PRACTICE EXPERIENCE

The Diabetic Multi-system Disease Prevention Initiative: One Team’s Approach

Background: Experience of a pre-dialysis multidisciplinary team

The Nephrology department, at the Saint John Regional Hospital serves approximately one-half of the Province of New Brunswick (pop. 729,498). Patients travel up to 3 hours to see the nephrology team.

The pre-dialysis clinic team consists of a nephrologist, a pharmacist, a nurse, a dietitian, and a consulting social worker. The goal of this clinic is to prevent further progression of patients' CKD, to optimize their pharmaceutical care and to prepare patients for dialysis. Patients are referred to the clinic when they have approximately 30% of their kidney function remaining (KDOQI Stage 4). There are approximately 250 patients in the clinic. This is greater than 100% more than 4 years ago with no additional resources. The proportion of patients in the clinic with type II diabetes is approaching 40%. The clinic experience has been rewarding. Many patients have maintained their remaining renal function over the past 4 years when literature would suggest that normal decline could be as high as 1 ml/min/month in patients with untreated diabetic nephropathy.⁵³

Despite these successes the pre-dialysis team recognizes that we are still reaching patients too late. Many type II diabetic patients referred to the clinic have not received proven interventions that can reduce their risks of cardiovascular events and progression of kidney disease. The team recognizes the need to reach patients earlier. It has also been noted that the majority of referrals come from areas closer to Saint John and that many patients are not being referred. To support this, a large number of new dialysis starts are patients that have never seen a nephrologist prior to starting dialysis. Early referral to nephrologists for type II diabetic patients has been identified as crucial not only for slowing the progression of renal disease but also for improving survival and morbidity on renal replacement therapy.⁴⁶

Unfortunately, the pre-dialysis clinic only reaches the "tip of the iceberg". Intervention needs to occur at the very early stages of CKD related to type II diabetes in order to have the greatest impact on patient outcomes.

A Strategy for New Brunswick

As discussed, it appears that emphasizing structure and continuous progression towards meeting multi-factorial goals may be the most important intervention in the treatment of type II diabetes. In New Brunswick there is a shortage of health care resources, and therefore, in order to impact care, a practical cost-effective approach is needed. In New Brunswick there is a shortage of both GPs and specialists. As a result GPs have very large practices, little access to specialists and long waits for specialized clinics. The task of managing a rising proportion of aging clientele, with an increasing incidence of type II diabetes is a tremendous burden on the GP. The team's goal is to facilitate the optimal care of these patients in a structured way and to give GPs access to the resources they need when they need it. Without additional resources for clinics to service the rest of

the “iceberg”, we needed to find a way to accomplish this in a realistic sustainable manner.

The Plan

The pre-dialysis team invited an endocrinologist, cardiologist, nurse clinician, and a diabetic educator to join our team. A Protocol was developed for the treatment of patients with diabetes at all stages of CKD. This Protocol includes desired targets and directions on dealing with unmet targets. (Sample Stage 1: Appendix A) The Protocol is based on the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (K/DOQI) guidelines for staging of CKD⁵⁴, Canadian Diabetes Guidelines⁵⁵, K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in CKD⁵⁶, K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD⁵⁷, the Canadian Hypertension guidelines⁵⁸, KDOQI guidelines for the management of anemia⁵⁹, and current best evidence. At each stage of kidney disease the Protocol becomes more comprehensive.

The Protocol will be produced electronically and allow for data entry by each physician office. As a target is identified as unmet, the physician will be directed to choose from a list of best-evidence first-line interventions (i.e. if patient has microalbuminuria, the physician will only have the option to choose an ACE or ARB that has proven benefits in the prevention of CKD progression). All data will be accessible by the project coordinator and analyzed upon completion of the three year pilot project

The Protocol is intended to be educational and serve as a road map for GPs in caring for the diabetic patient with CKD at all stages. At each step of the Protocol, there are indications for referral if the patient is experiencing complications with regard to their disease or fails to meet pre-defined targets after three visits to the GP.

A quick-referral interdisciplinary clinic will be held bi-monthly in Saint John, NB to manage patients referred from the GP according to the Protocol. This clinic will be supported by a renal nurse, pharmacist, dietitian, diabetic educator, nephrologist, endocrinologist, and a cardiologist as required. Recommendations will be made back to the GP in regards to the patients' care and the GP will continue to provide care for this patient based on the Protocol.

As patients draw closer to dialysis they will be seen more frequently by the nephrology team in the already established pre-dialysis clinic.

The Protocol will be promoted to GPs, nurses and pharmacists in key locations throughout the province as an initial 3-year pilot project. Education sessions will be held for all groups throughout the province.

In addition to the Protocol, GPs will also be provided with a “toolkit” in the form of an interactive CD that includes all of the guidelines and references used the development of the Protocol. This CD will also include printable patient resources for understanding modifiable risk factors and what they can do to impact their outcomes.

Our goal at the end of the 3 years is to have our strategy implemented province wide and to be financially maintained by the provincial government. We hope that a GP focused approach to disease management will prove to be a feasible and economic model for the future.

Primary Objectives for Evaluation:

- Describe the change in referral patterns of patients with diabetes and CKD using pre-defined laboratory parameters.
- Describe the role of the interdisciplinary clinic in the management of the diabetic patients with CKD based on predefined workload indicators.
- Describe the level of satisfaction of GPs with the initiative using a survey at predefined times during the pilot project.
- Evaluate cardiovascular and renal outcomes in these patients and compare to literature controls and data from the Canadian Organ Replacement Registry using pre-defined definitions for cardiovascular and renal events.

Limitations

Our evaluation of this project will be limited to observational data from our patient population. We are unable to feasibly randomize patients to this intervention or standard care without affecting the control group. However, we will be able to compare referrals received by target physician offices to those that come from physicians not involved in the project.

Success to Date

- The Protocol and toolkits are almost complete. The Protocol needs to be reviewed by the team again prior to circulation for changes in light of new evidence (i.e. CARDS trial³⁰).
- We have presented our project to industry stakeholders, seeking research grants for the initial pilot project. We have received a significant component of our needed funding and several verbal commitments for the remainder.
- We have presented our project to government stakeholders, seeking a commitment to long-term maintenance of this project, should the pilot be

- successful. We have received a commitment of space and shortfall security for the pilot, in addition to a long term commitment.
- We have gained approval from other nephrology centres in the province for long-term commitment to this model should the pilot prove successful.
 - We have contracted an IT company to build the software for the program.
 - The strategy was presented the model at the New Brunswick Pharmacy Conference in June 2006.
 - The expected implementation date is September 2006.

PRACTICE REFLECTION

The greatest reward in the process has been working with committed and enthusiastic team members to work towards a vision with the goal of improving patients' lives.

CONCLUSION

The five studies reviewed suggest that long-term, targeted, structured intervention involving multiple risk factors reduces the risk of both cardiovascular and renal events in patients with type II diabetes. More research is needed to identify the most effective model of delivery of multi-factorial interventions.

As a result of this review a strategy to improve renal and cardiovascular outcomes in patients with type II diabetes in New Brunswick was developed. The Diabetes Multi-System Disease Prevention Initiative offers a potential model of care that involves both the GP and a quick referral multi-disciplinary team to offer an innovative, practical and affordable solution to the growing epidemic of cardiovascular and renal disease caused by type II diabetes in New Brunswick. Should this model prove successful, it is a model that could be applied to other chronic disease state management strategies in New Brunswick.

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Table 1

Effects of Multi-factorial Intervention Models on Cardiovascular and Renal outcomes in Patients with Type II Diabetes.

Study Ref	Hanefeld et al. <i>Diabetes Care</i> 14:308-17, 1991 ⁴⁸	Gaede et al. <i>Lancet</i> 1999;353:617-22 ⁴⁹	N. Joss et al. <i>QJMed</i> 2004;97:219-227 ⁵⁰	Olivarius et al, <i>BMJ</i> 2001;323:1-9 ⁵¹	Rachmani et al. <i>Diabet Med</i> 2005;22:410-414 ⁵²
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Table 1. Description of clinical trials evaluated.

Study Name	Diabetes Intervention Study	Intensified multi-factorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: The Steno-2 randomized study	Intensified treatment of patients with type 2 DM and overt nephropathy	Randomized controlled trial of structured personal care of type 2 diabetes mellitus	Teaching and motivating patients to control their risk factors retards progression of cardiovascular as well as microvascular sequelae of Type 2 diabetes mellitus-a randomized prospective 8-year follow-up study
Date of Study Period	Screening from 1977-1980, 5 year follow-up (based on 1977 guidelines)	Screening from 1992-1993 (Based on 1985 guidelines) Study completed in 1997	Not stated	Enrollment from 1989-1991	Recruitment 1995-1996
Study Design	A randomised, prospective 5-yr multi-intervention trial	A randomised, open, parallel trial. Mean follow-up was 7.8 years	2-year multi-centered, prospective randomised-controlled study comparing intensive medical management to	Pragmatic, open, controlled trial with randomisation of practices to structured personal care or routine care. Analysis after 6	Randomised prospective study, mean follow-up 7.7 years

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			routine practice	years	
Number of Subjects	1139	160	90	874	141
Patient Population	Newly diagnosed NIDDM, aged 30-55 from 16 diabetic clinics in Germany. Patients without previous MI, stroke, gangrene or "other severe life-limiting illness"	Patients recruited from one diabetes centre in Copenhagen. Patients had microalbuminuria (30-300mg/24 hrs) and Type 2 diabetes, age 40-65. Pt's excluded for pancreatic insufficiency, alcohol abuse, non-diabetic kidney disease, malignance or life-threatening illness with prognosis of < 4 yrs.	Pts with type 2 diabetes and albuminuria > 300mg/24 hours	All patients age 40 or older with newly diagnosed diabetes from 311 Danish practices. Patients were excluded for life threatening somatic disease, severe mental illness, or unwillingness to participate. Non-white patients were excluded in this published analysis.	Pts with Type II diabetes mellitus, hypertension (>140/90 mmHg) and hyperlipidaemia (LDL-C > 3mmol/L), referred for consultation to a single diabetes clinic and academic hospital in Tel-Aviv.
Description of Intervention(s)	Patients were divided into three groups. 1) control with standard care by local diabetes clinics 2)	Randomly assigned to standard treatment by their general practitioner or intensive multi-	The intensive group was seen as often as necessary by the project team (doctor, nurse and dietitian). The control were	Practices were randomised to routine care (control) or structured care (intervention).	Control group received standard consultation visits, Participants in the intervention group were give two 2-

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	Intensive health education (IHE) on weight loss, lipid lowering diets, physical activity, smoking cessation, and management of hypertension 3) IHE + clofibrate 1.6 G/day after 2 years of trial Patients in intervention group were seen every 3 months	factorial intervention with behaviour modification and stepwise introduction of pharmacological therapy. Project team included doctor, nurse, and dietitian. Interventions included: Dietary fat < 30%, Saturated fat < 10%, exercise 30 min 3-5x/week, smoking cessation. ACEI, Vitamin C and E, ASA, AIC< 6.5%, SBP<140, DBP<85, Trig < 1.7mmol/L, Total Chol < 5.0 mmol/L, HDL 1.1 mmol/L	see at their usual clinic. Treatment goals were identical. SBP < 140 mmHg, DBP < 80 mmHg, HbA1c < 8%, Na intake < 120 mmol/day, protein intake 0.7-1 g/kg/day, Chol < 4 mmol/L, Chol:HDL ratio < 4 mmol/L. Exercise was encouraged, advice given on smoking cessation.	Intervention group were followed up every 3 months and individualized goal setting supported by prompting of doctor, clinical guidelines, feedback and continuing medical education.	hour individual education sessions on modifiable risk factors, a plan for change, a fitness program, blood pressure monitor with instructions to monitor weekly. They were given their lab results and encouraged to address them with their family MD to meet targets. (BP < 130/80; LDL-Chol < 2.6 mmol/L, HbA1C < 7%). Patients were given direct access to consultants and reinforcement of education and motivation took place with each additional visit. Care was carried out primarily by
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					family physician.
Primary Outcome	Reduction in level of coronary risk factors and incidence of IHD	Primary outcome with the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, non-fatal stroke, amputation resulting from ischemia, or vascular surgery for peripheral atherosclerotic artery disease.	Rate of progression of renal disease in second year of follow-up	Predefined clinical outcomes: overall mortality, incidences of diabetic retinopathy, urinary albumin concentration > 15 mg/L, myocardial infarction, and stroke in patients without these outcomes at baseline	Cardiovascular disease, retinopathy, and decline in GFR
Secondary Outcome(s)	Behaviour (caloric intake, fat consumption, cholesterol, alcohol intake, physical activity,	Development of diabetic nephropathy, development or progression of diabetic	Changes in clinical data	New peripheral neuropathy, angina pectoris, intermittent claudication and amputation.	

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	smoking)	retinopathy, and progression of neuropathy		Risk factor levels	
Major Findings	Significant improvement in fasting glucose control (9.27mmol/L vs. 8.71mmol/L; p=0.01), exercise scores (174 vs. 327 p=0.01), blood pressure, tobacco and alcohol consumption. No benefit in caloric intake, fat intake, body weight, IHD, MI, ECG changes, or death. Increase in Total cholesterol in all groups. Clofibrate group had significant decrease in triglycerides only.	Intensive treatment was associated with lower risk for primary composite endpoint (NNT=5 over 7.8 years), development of diabetic nephropathy (NNT=6), development or progression of retinopathy (NNT=7) and progression of autonomic neuropathy (NNT=5). Study was non-significant for progression of peripheral neuropathy. Hypoglycemic events did not differ between	Median rate of loss or renal function for intensive group was 0.44 ml/min/month in year 1 and 0.14 ml/min/month in second year compared to 0.49 ml/min/mo in year 1 and 0.56 ml/min/month in year 2. This was statistically significant. (p=0.04) Significant differences between groups were demonstrated for the following parameters: SBP (164 vs. 143; p=<0.001), DBP(82 vs. 73; p=<0.001), Albumin:creatinine	No difference in predefined non-fatal outcomes and mortality. Improvement in fasting glucose concentration, glycated HgB (8.5% vs. 9%;p=0.0007), SBP (150 vs. 145; p=0.0004), and Cholesterol (6.1 vs. 6.0mmol/L p=0.029), and weight loss 2.0 vs. 2.6 kg.	The average annual decline in e-GFR was 4.6 ml/min/year and 3.0 ml/min/year in the control and treatment groups respectively (P=0.01) Significantly more patients developed overt nephropathy in the control group (RR=0.5; p=0.02) during study period. Retinopathy was significantly more prevalent in the control group (RR=0.6; p=0.03) The total number

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		groups	ratio (119 vs. 67 mg/mmol/L), Total cholesterol (5.1 vs. 4.4; p< 0.01), Chol:HDL ratio (5.3 vs. 4.5 mmol/L p=<0.05)) and sodium intake Additionally: Patients in the intensive treatment had significantly fewer hospitalizations(62% vs. 47% p=0.05), shorter lengths of stay and fewer new cardiovascular events (21 vs. 13, p=0.038) than controls		of fatal and non-fatal CVD events was 80 vs. 52 in the control and treatment groups respectively (RR=0.65; p=0.001). There were statistically fewer strokes in the treatment group (RR=0.47;p=0.01) and fewer coronary events and interventions (RR=0.70; p=0.005)
Comments	Older study, pre-UKPDS findings. Standard of care was diet for glycaemic and cholesterol		Hospitalizations and cardiovascular events were not predefined outcomes in this trial	Diabetic Care was primarily carried out by the General Practitioner for both intervention and control groups	Cardiovascular outcomes were not clearly defined in the study methods.

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	control, patients were predominately followed by specialists, not family MD as they are now. Definitions for cardiac outcomes were poorly defined				
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Appendix A
Draft Protocol (Manual Version)