Evaluation of a pharmacist-led cardiovascular risk clinic for patients with diabetes attending a hospital out-patient clinic

A partial fulfilment of the Norwegian degree
Master of Pharmacy
University of Tromsø, May 2012

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Acknowledgment

I would like to express my sincere gratitude to all whom participated and helped me to conduct my study and carry out my thesis
I would like to thank my academic supervisor Moira Kinnear, my direct supervisor Alison Coll and my clinical supervisor Alison Cockburn for all the help and guidance.
I also would like to thank the administrator, Elaine Blackie and all staff members working in the Education, Research & Development department at the Western general hospital. Your help and input is much appreciated.

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Abstract

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Background

Cardiovascular disease is strongly associated with diabetes and is a major cause for disability and mortality among diabetic patients. Hypertension is prominent in diabetic patients, especially type 2 diabetics and 50% are receiving suboptimal hypertension treatment. In NHS Lothian, reducing blood pressure for hypertensive diabetic patients presented a challenge. A potential solution was to utilise the clinical pharmacist to solve this problem and in 2003 a pharmacist-led cardiovascular risk reduction clinic was established for that purpose. Initial evaluation suggests a promising reduction in blood pressure, lipid levels and improved prescribing quality but a comparison with usual care has not been conducted through a prospective randomised controlled trial.

Aim

The aim of this study was to evaluate the feasibility of outcome measures to inform a future prospective study to evaluate the pharmacist-led clinic and to measure the impact of the clinic on cardiovascular risk reduction and the outcome of this intervention in terms of reduction in blood pressure, number of patients reaching target blood pressure and hospital admissions after discharge.

Method

Patients attending the pharmacist-led clinic were labelled the intervention group. A list of patients discharged from the clinic before 2009 was supplied by the pharmacist. Patients attending the usual care were labelled the control group and were chosen from lists of patients who had hypertension (BP>130/80mmHg) and/or microalbuminurea (ACR >3.5 mmol/L).

A spreadsheet was designed to be populated with patients' information such as baseline characteristic at first visit, co-morbidities, physiological parameters, drug history, drug therapy problems, guidelines adherence and hospital admission after discharge. The process of data collection was performed retrospectively by case note review.

Results

Forty five patients were included in the intervention group and 42 in the control group. There were significant differences in baseline characteristics in terms of age ($p=0.0006$), duration of diabetes ($p=0.003$), HbA1c ($p=0.026$) and number of comorbidities (p0.022). The results showed a greater significant reduction in systolic blood pressure ($p=0.0088$) and a significant number of patients reaching target blood pressure ($p =0.0036$) in the intervention group. Reduction in diastolic blood pressure, ACR and total cholesterol was insignificant.

The study also showed a significant difference in the number of antihypertensives started or increased ($p<0.001$) and a significant difference in the number of medication related problems actioned ($p=0.0058$). There were a greater number of hospital admissions among the intervention group. Reduction in systolic BP, reduction in diastolic BP and proportion of patients reaching target BP were used to calculate a potential sample size for a prospective study.

Conclusion

Data collection proved challenging and barriers will have to be overcome in terms of access to follow up data in a prospective study.

Reduction in blood pressure and the proportion of patients reaching target blood pressure change in pharmaceutical care plan drug therapy problems actioned can be used as an outcome measure and primary end point in the future study.

Reduction in ACR and the number of hospital admission might be used as a feasible outcome measure if the intervention and the control group in the future study are similar and randomised correctly.

Abbreviation list

ACE	-	Angiotensin converting enzyme
ACR	-	Albumincreatinine ratio
AMP-kinase	-	Adenosine monophosphate kinase
ARB	-	Angiotensin-II receptor blocker
BMI	-	Body mass index
BNF	-	British National Formulary
BP	-	Blood Pressure
CBVD	-	Cerebrovascular disease
CCBs	-	Calcium channel blockers
COPD	-	Chronic obstructive pulmonary disease
CVD	-	Cardiovascular disease
DBP	-	Diastolic blood pressure
DCVR	-	diabetes cardiovascular risk
DM	-	Diabetes mellitus
DRP	-	drug related problems
GDM	-	Gestational diabetes mellitus
GP	-	General Practitioner
HbA1c	-	Glycated hemoglobin
HDL	-	High-density lipoprotein
HOT	-	Hypertension Optimal Treatment
IT	-	information technology
LDL	-	Low-density lipoprotein
MRP	-	Medication related problems
NHS	-	National Health Service
PVD	-	Peripheral vascular disease
RCT	-	randomised controlled trials
SBP	-	Systolic blood pressure
SCI-DC	-	Scottish Care Information - Diabetes Collaboration
SIGN	-	Scottish Intercollegiate Guidelines Network
UK	-	United Kingdom
WHO	-	World Health Organisation
WGH	-	Western General Hospital

1. Introduction

1.1 Pharmaceutical care

In 1990 Hepler and Strand defined pharmaceutical care as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. These outcomes are (1) cure of disease, 2) elimination or reduction of a patient's symptomatology, (3) arresting or slowing of a disease process, or (4) preventing a disease or symptomatology"[1]

Pharmaceutical care is not a term used to describe the profession of pharmacy, but rather a process of collaboration between different healthcare givers and the patient. The main objective of this process is to ensure direct benefit of the patient. A pharmaceutical care plan identifies the patient's medical conditions and patient's drug-related needs, detects problems with drug therapy, develops an action plan and monitors to ensure the safety and effectiveness of the plan [2].

Throughout the last century the profession of pharmacy has gone through fundamental changes. The big pharmaceutical companies took over medication production and ensured faster and more efficient distribution of medications to the population, the profession of pharmacy channelled into new fields, the bases of the profession became more patient centred rather than medicine centred.

When drugs are given to patients there is always a possibility of undesired outcomes due to drug-related problems. There are several causes that could lead to drug-related problems, these causes can be categorised into five criteria: suboptimal prescribing, suboptimal delivery of medicines, patients compliance, patients views on medications and suboptimal monitoring [1]. Drug related problems are a burden for treatment and a costly social problem

Due to their education and training, pharmacists play a vital role in pharmaceutical care. The cost of drug-related morbidity and mortality causes a substantial strain to the health system. It also forces new demands to improve pharmaceutical care and

improve health services offered to patients. All these factors gave the profession of pharmacy a leading role in pharmaceutical care, taking into account that these problems could be avoided using pharmaceutical knowledge.

1.2 Chronic diseases worldwide

The prevalence of chronic diseases is increasing and is a leading cause of death worldwide. The diseases affect all socioeconomical classes, but are mainly afflicting low and middle income class. Chronic diseases account for 63% of the mortalities worldwide, low to middle income countries account for 80-90% of cardiovascular, diabetes and chronic obstructive pulmonary disease (COPD) deaths worldwide. According to the World Health Organisation (WHO) the devastation afflicted by chronic diseases can be reduced drastically by reducing four main risk factors; smoking, physical inactivity, harmful alcohol consumption and unhealthy diet. Compliance was documented as an issue whereas only 50 % of patients comply with their medicines [3].

The populations in low to middle income countries are subjected to uncontrollable marketing for tobacco, alcohol and junk food and most governments fail to regulate marketing leaving the population disposed to unhealthy marketing. The expenses of chronic disease treatment which is not covered by health plan is also a cause for the high mortality and morbidity, it forces patients to cover all medical expenses which puts a strain on the patient's budget.
In order to improve the outcome of chronic diseases the health systems worldwide must step in to monitor exposure, monitor morbidity and mortality of chronic disease and adapt plans and health policies to deal with the magnitude of chronic diseases [3].

1.3 Patient's journey in the UK vs. patient's journey in Norway:

In the United Kingdom (UK); the diagnosis of diabetes take place mainly at General Practitioner's (GP) clinics in primary healthcare; the patient's medical needs and health are assessed by the doctor responsible for the patient. Patients can be referred

to the hospital to be treated at the diabetes clinics. Educational programs held by nurses are offered to the patients to improve their understanding of the disease. The role of the nurses extends beyond educational and motivational; they also play a role in monitoring and treating patients.
In order to improve health services and improve patients' access to medications the Scottish government granted nurses, pharmacists and other allied health professionals the right to prescribe medicines (non-medical prescribing) following accredited education and training [4].
The diabetes patients can be referred to an ophthalmologist, a podiatrist, an endocrinologist or a nephrologist to prevent or to treat diabetes complications. Patients can also be referred to cardiovascular risk reduction clinics led by pharmacists to prevent and treat cardiovascular diseases associated with diabetes. These clinics offer optimisation of medical regimen, intensive care and monitoring, and frequent follow up for the patients.

In Norway the diagnosis of diabetes take place at primary care; GPs or primary health clinics. The patients can attend educational programs introduced by diabetes nurses. Patients can also be referred to a dietician and physiotherapists to improve diet and to devise a plan for exercise. The monitoring and the assessment of patients are usually undertaken by the doctor. If the patients require special needs or the disease exacerbates they can be referred to the secondary healthcare where specialists in endocrinology, cardiology and nephropathy assess and determine the appropriate treatment regimen for the patients.

The diabetes services in Norway are not as diversified as in Scotland; there is no legislation to support non-medical prescribing. Nurses-led clinic and pharmacists-led clinics do not exist in Norway. Still, the clinical pharmacists are a part of a collaborative team to offer a complex intervention. They are utilised to optimise treatment and enhance the pharmaceutical care.

1.4 Diabetes mellitus

Diabetes mellitus (DM) is a chronic endocrine disorder affecting the metabolism of carbohydrates, proteins and lipids. It is characterised by impairment in production of insulin with or without insulin resistance. Insulin is a hormone produced by β-cells in the pancreas, it plays a major role in metabolism of carbohydrates, proteins and lipids, as it facilitates uptake and storage of these components into the cells [5]. Lack of insulin or resistance to it leads to hyperglycaemia (increased sugar levels in blood), which constitutes the major finding in diagnosis of DM. There are three types of DM: type 1 DM, type 2 DM and gestational DM (GDM). GDM is characterised by insulin resistance during pregnancy [6].

1.5 Type 1 diabetes mellitus

Type 1 DM accounts for 5-10 % of patients with diabetes and it may present at any age, but the majority of the patients will experience it at puberty [6]. This disorder rises from destruction of β -cells in the pancreas which in 90% of the cases is due to autoimmune disease involving T-cell mediated destruction, the destruction of β-cells leads to reduced production of insulin. The rate of β-cell destruction varies in individuals being fast with some and slow with others. In addition some patients with diabetes will present with ketoacidosis as first sign of the disorder [6]. Ketoacidosis is an acute emergency: fat, in anaerobic metabolism, is broken down to β -hydroxybuterate (which causes the acidosis) and acetone, which is a ketone [7].

1.6 Type 2 diabetes mellitus

Type 2 DM is the most common type of diabetes, it accounts for 90-95 % of all diabetic patients. The disorder is more common among adults and the incidence of the disease rises with increasing obesity [6]. The aetiology of this disorder is not fully understood and unlike Type 1 DM, β-cells destruction is not involved. The onset symptoms are much slower than that of DM type 1. It is characterised by insulin resistance and inadequate insulin secretion [6].

1.7 Epidemiology of diabetes mellitus

The percentage prevalence of DM is 8.3% worldwide and the number of diabetic patients worldwide is estimated to be 366 million in the year 2011. The number is estimated to increase to 552 million by the year 2030 with global prevalence of 9.9% [8]. Eighty percent of these diabetic patients live in developing countries and 183 million people with diabetes are undiagnosed [8]. The rate of mortality due to DM worldwide is estimated at 4.6 million deaths in 2011 and the disease cost at least 465 billion dollars in health expenditure in the year 2011 and the rate of diabetes morbidity and mortality keeps increasing every year [8].

In Scotland the number of patients diagnosed with diabetes is estimated to be more than 228,000 which is 1 in 25 of the Scottish population, and there are at least 2000 patients who are undiagnosed [9]. It is estimated that 27000 people in Scotland have type 1 DM which accounts for 13% of all diabetic patients. More than 80% of diabetic patients have type 2 DM and the number of people with type 2 DM in Scotland is currently increasing at a rate of 4% per year. Diabetes requires a great deal of care and long term management due to multiple complications, the diabetes is thought to account for 10% of the total Nation Health Service (NHS) Scotland expenditure [9].

According to the Lothian diabetes register of 2010, the number of diabetes patients in NHS Lothian is more than 32,000 people constituting more than 4% of the NHS population and 86.7 % of diabetes patients have type 2 diabetes[10].

1.8 The cost of diabetes

DM accounts for 10% of the NHS UK budget which is estimated to be 9 billion pounds based on 2007/2008 NHS budget. In the UK, it is estimated that 1 in every 10 hospital admissions is caused by DM or long term complications related to DM. According to Diabetes UK in the year 2008, 28.4 million medications for DM treatment were prescribed at a cost of £ 561.4 million and diabetes prescribing now accounts for 7 % of all prescription costs [11]. Due to complications and prolonged

monitoring requirements diabetes patients occupy approximately 80,000 bed days per year in the UK [11]. In addition the presence of diabetes complications increases the cost of social services by four fold. In Scotland, diabetes accounts for 5% of the NHS expenditure. In 2002/2003 the diabetes cost was estimated to be 32 million pounds [12].

1.9 Diabetes complications

There are multiple complications associated with diabetes; the complications can be divided into acute and chronic. The acute complications are polyuria, polydipsia, weight loss and ketoacidosis which can be life threatening [6]. The long term complications arise from poor diabetic control and presence of risk factors. Risk factors include obesity, unhealthy lifestyle, physical inactivity, smoking and heavy alcohol consumption. The complications can be divided into macrovascular (damage to the large blood vessels) and microvascular (damage to the small blood vessels) [13].

1.10 Macrovascular disease

There is a significant increase in macrovascular complications in patients with diabetes. Macrovascular complications are cardiovascular disease (CVD), peripheral vascular disease (PVD) and cerebrovascular disease (CBVD). Cardiovascular disease is the most common cause of death for diabetes patients. Factors that will increase the probability of CVD are smoking, dyslipidemia, hypertension and nephropathy. The incidence of CVD is greater in patients with diabetes than in those without diabetes. CVD is responsible for increased mortality rate and reduced life expectancy in this patient group. The reduction of CVD risk can be achieved by intensive glycaemic control, reduction in blood pressure (BP) to a target level and reduction of dyslipidemia to a target level [13].

PVD affects blood vessels outside the heart, mainly the legs and the feet; PVD is associated with atherosclerosis and thrombosis leading to neuropathic pain in the legs and loss of feeling in the feet. Approximately 20% of diabetes patients with PVD die of myocardial infarctions within two years of symptom onset. Cerebrovascular

disease is caused by atherosclerosis. Atherosclerosis followed by plaque formation leads to occlusion and reduction in blood flow and thrombosis which also leads to stenosis of the intracerebral arteries. The BP fluctuation and the embolism can cause ischemic stroke damaging the blood vessels and causing intracranial haemorrhage [14].

1.11 Management of diabetes

Diabetes management is a complex intervention. This intervention aims to offer medical and non-medical therapy options for the patient. Non-medical therapy includes lifestyle advice on diet, exercise, smoking cessation and reducing alcohol consumption [13].

1.12 Lifestyle factors

Patients with DM are offered lifestyle changing advice to help them in controlling the disorder. This support can be in the form of education programmes or consultations with dieticians to promote healthy lifestyle and discourage unhealthy habits. Patients who have poor diet and are obese should be encouraged to reduce fat, sugar and carbohydrate intake in order to achieve healthy weight and normal body mass index (BMI) [13]. Physical activity should be encouraged regardless of BMI status. Exercise and physical activity can help prevent CVD and reduces hyperglycaemia and dyslipidemia. Unhealthy habits that affect quality of life should be discouraged. Smoking is hazardous to health and is a major contributor to CVD; in addition it is a major factor preventing physical activity. All smokers should be advised to cease smoking [13]. Patients who consume alcohol should be advised to reduce alcohol consumption. The alcohol limit for men is no more than 4 units in any one day and for women is no more than 3 units of alcohol in any one day.

1.13 Medical management of Hyperglycaemia

Intensive glycaemic control is associated with reduction in microvascular and macrovascular complications associated with DM. Macrovascular disease risk increases when Glycated hemoglobin (HbA1c) exceeds 8% which is the upper normal

reference value. Hyperglycaemia can be diagnosed by directly measuring blood sugar levels or by measuring HbA1c which indicates the blood sugar levels for the last 8-12 weeks. A 1% increase in HbA1c leads to 11% increased risk for CVD [13].
Oral anti-diabetic drugs and insulin preparation are used to control hyperglycaemia. Patients with type 1 diabetes can only be managed with insulin preparations whereas patients with type 2 diabetes can be prescribed either oral anti-diabetic and/or insulin preparations. The two main classes of oral anti-diabetic drugs are biguanides and sulfonylureas.

Biguanides (eg Metformin) activate the enzyme Adenosine monophosphate kinase (AMP-kinase) in the liver which leads to reduced hepatic output of glucose and improves peripheral glucose disposal. Metformin is considered the first line oral treatment for overweight patients with type 2 DM because it suppresses the appetite and promotes weight loss [13].

Sulphonylureas (eg Gliclazide) increase endogenous release of insulin from pancreatic β-cells and increase tissue sensitivity to improve the action of insulin. Sulphonylureas may also promote increased systematic bioavailability of insulin due to reduced hepatic extraction of insulin secreted from the pancreas. Side effects include weight gain and higher probability of hypoglycaemia compared to metformin. Sulphonylureas should be considered as first line treatment for non obese patients or patients who do not tolerate metformin [13].

There are other types of oral anti-diabetic drugs that are used less frequently, these can be used in combination with metformin or sulphonylureas or could be used alone. The mechanism of action varies, some amplify insulin secretion (eg saxagliptin), others enhance the action of insulin (eg pioglitazone) and some inhibit carbohydrate digestion (eg acarbose) [13, 15].

1.14 Hypertension and cardiovascular risk reduction

Hypertension is strongly associated with diabetes, mainly with type 2 DM; it is also an independent risk factor for macrovascular and microvascular complications associated with diabetes. Studies have shown the risks of hypertension: a 5 mmHg

increased in diastolic blood pressure (DBP) can lead to 20-30% increase in cardiovascular disease [16]. The threshold for hypertension differs between the diabetic population and the rest of the population, due to the risk of cardiovascular disease associated with diabetes. The threshold for non-diabetic patients is 140/90mmHg while for diabetic patients it is 130/80mmHg.

In a Hypertension Optimal Treatment (HOT) randomised trial: 1501 patients with DM were randomised into three groups: BP ≤ 90 mmHg, BP ≤ 85 mmHg, BP ≤ 80 mmHg. Cardiovascular events in the BP ≤ 80 mmHg group were halved compared to the BP ≤ 90 mmHg group. It also demonstrated a reduction in myocardial infarction, stroke and cardiovascular mortality. The results presented by the HOT study became adapted as a general definition for hypertension in diabetes treatment guidelines [17]. The systolic threshold of 130 mmHg is a locally approved limit for systolic blood pressure (SBP).
Hypertension can present itself at different stages of the disease. For type 1 diabetics hypertension is present in approximately 30% of the patients and takes time to ensue up to several years after the diagnosis. Hypertension in type 2 diabetics can be presented before the development of the disease due to patients being older and generally overweight [16].

Hypertension should be treated aggressively with lifestyle modifications and medical treatment. Drugs incorporated into treatment guidelines are usually selected according to BP reduction properties, cardiovascular risk reduction properties, nephropathy reduction and renal function improvement properties and adverse drug reactions. Diuretics have demonstrated a BP lowering property, mainly by elimination of sodium from the body. Until recently, a thiazide diuretic was first line. Beside the diuretic effect it has shown a vasodilatory effect. The main adverse drug reaction is hypokalemia and as renal function worsens, thiazides become ineffective as it is associated with lose of renal function. Loop diuretic (Furosemide) is a subclass of diuretics, just like thiazide, it also has a vasodilatory effect. It can be used instead of thiazide if the renal function deteriorates [16].
The Renin-Angiotensin-Aldosterone Axis is a system in the body involving many organs utilized to balance electrolyte levels and fluids in the body, making it a vital target for antihypertensive medications. Angiotensin-converting enzyme (ACE)

inhibitors can be used as first line treatment for hypertension in diabetic patients. ACE-inhibitors lower BP and slow the progression of renal disease by reducing the rate of progressive loss of glomerular filtration rate independent of level BP reduction[18]. ACE-inhibitors are effective in preventing nephropathy and retinopathy [16]. ACE-inhibitors inhibit bradykinin degradation which can cause dry cough forcing patients to switch to Angiotensin receptor Blockers (ARB). ARBs induce blood pressure reduction through the same system as ACE-inhibitors and possess the same renal protective action as ACE-inhibitors, but do not inhibit Bradykinin.

High levels of circulating aldosterone lead to increased BP through fluid retention and increased albuminuria. Aldosterone blockers (Spironolactone) have demonstrated effectiveness in BP reduction when used in combination with ACE-inhibitors and reduction in albuminuria [19]. Because of severe hyperkalemia, aldosterone blockers cannot be used as monotherapy and are not first line treatment agents.

Calcium channel blockers (CCBs) bind to calcium channels located on the membrane and block the influx of calcium leading to vasodilatation. CCBs are effective in reducing BP and are used in combination with ACE-inhibitors or ARBs [18]. Oedema is a common side effect of the CCBs especially in the ankles.

β-Blockers are the least effective anti-hypertensive agents and less effective at preventing stroke than other agents [18]. β-Blockers are not suitable for initial hypertension treatment due to observed increase in cardiovascular mortality [13].

α-blockers are not suitable for initial hypertension treatment due to observed increase in heart-failure. They are used for patients who cannot reduce their BP with first line treatment.

1.15 Dyslipidemia and cardiovascular risk reduction

Dyslipidemia has a strong association with type 2 diabetes. Many patients are characterized with obesity, low High-density lipoprotein (HDL), high Low-density lipoprotein (LDL), high cholesterol and triglycerides. Dyslipidemia is considered as a

risk factor because of the presence of small dense LDL-particles and oxidation of glycated LDL-particles [5]. These abnormalities accelerate the atherogenesis progression, damaging the heart muscle and blood vessels. Statin treatment for lowering lipid levels is recommended as first line prevention of CVD for type 1 and type 2 diabetic patients whom are older than 40 years regardless of the cholesterol baseline. Statin therapy (whether Simvastatin 40mg or Atorvastatin 10 mg) is shown to reduce cardiovascular events comprising stroke, acute coronary events and coronary revascularisations [13]. This reduction of cardiovascular events arises from the different action modes of statins as they, improve endothelial function, reduce vascular inflammation, reduce platelet aggregability, increase neovascularisation of ischemic tissue, increase circulating endothelial progenitor cells, stabilisations of atherosclerotic plaque and antithrombotic actions [5].

1.16 Pharmacist-led diabetes cardiovascular risk clinic

In NHS Lothian, despite the development of prescribing guidelines and patients' attendance at hospital specialist out-patient clinics, achieving target BP continued to be a challenge. The pharmacists' role in pharmaceutical care was considered a potential solution to this challenge and a pharmacist-led diabetes cardiovascular risk (DCVR) clinic was established in 2003 within primary and secondary care sites in NHS Lothian. The clinics were established using short-term funding and aimed to monitor, treat and reduce the risk factors that lead to CVD in diabetic patients. The clinic has shown promising results in reducing BP, lipid levels and HbA1c and established funding continued to allow three clinics in NHS Lothian at three different sites. Limited funding limits the number of pharmacists working in the clinics, limiting the number of patients seen by the clinics and the time dedicated for every appointment. Some of these clinics operate once a week others are limited to once a month.

The referral criteria to the clinic are broad and may not guide physicians who are less familiar with the clinic than those involved in its establishment. Referred patients tend to be hyperglycaemic, hypertensive and dyslipidemic. These patients are considered resistant to treatment and are at high risk of developing cardiovascular complications.

In the initial consultation, BP measurements are taken, the medical history of the patient and medication list is confirmed. There are approximately 60 patients referred to the pharmacist-led clinic per annum.
The pharmacists in the clinic have access to the electronic patient record database SCI-DC (Scottish Care Information - Diabetes Collaboration) to obtain medical record, patient's history and blood and urine analysis results of the diabetic patient [20]. The SCI-DC project started in 2002 to improve diabetes services in NHSScotland. The aim of the project was to introduce an information technology (IT) system for diabetes care, an electronic patient record database and all involved in diabetes care are granted an access to the program. The patient's medication adherence is also assessed. Blood and urine samples are collected in order to work up a pharmaceutical care plan [21]. The pharmacist in collaboration with the diabetes physicians has developed guidelines for reduction of cardiovascular disease risk. The first guideline was used in 2003 until 2005, second guideline used between 2005 and 2010 and the latest guideline was developed in 2010 and is still being used (see appendix 1). The pharmacist in cooperation with the diabetic consultant recommends changes to the prescribed medicine regimen, either by increasing a dosage, commencing a new medication or stopping medication the patient is currently using. These recommendations are usually sent to the GP responsible for the patient to commence in primary care. The pharmacist sends the letter using the same process as letters would be sent from the specialist physician. In NHS Scotland no prescribing takes place in the out-patient clinic, recommendations are made to the GP for continued prescribing for chronic diseases.

Due to limited number of staff, limited time for each consultation and the great number of diabetic patients, the patients are followed up approximately once every six weeks until target BP is achieved or no further improvement can be obtained [21].

Usual care – patients who are not referred to the pharmacist-led clinic are seen by the physician in the diabetes unit. The main focus of the physicians is to initiate and optimise diabetes treatment. However they can make changes to the antihypertensive and cardiovascular treatment. The usual care can offer appointments to more than 3000 patients per annum, but not as frequent as the pharmacist-led DCVR clinic. Depending on diabetes control, usual care can offer two to three appointments per

annum for patients with poorly controlled diabetes. If diabetes is under control patients are offered a single appointment every year, patients are seldom discharged, unless request to be discharged, they still receive appointments. The treatment protocol used in the usual care is vague and not as well defined as the treatment protocol used by the pharmacist-led DCVR clinic (treatment guideline for diabetes clinic included in appendix 2).

1.17 Previous work to evaluate the pharmacist- led DCVR clinic

A small audit, in which 10 patients were interviewed to explore their views on the clinic showed that most patients reported being satisfied with the service provided and can report better understanding of hypertension and antihypertensive treatment also that most patients increased their understanding of better healthy lifestyle, but only few committed to change their lifestyle [22].

In a study of 40 patients assessing the cardiovascular risk reduction showed a decrease in clinical BP upon clinic entry, discharge and follow up. The study also showed a decrease in lipid values, change in the total number of antihypertensive medications and dose increase of antihypertensive, also a change in type of statin or dose increase [21]. In order to eliminate bias and other variables that could affect the BP monitoring the patients were given a 24-hour ambulatory BP monitoring device. A significant decrease with an average of 13/9 mmHg was recorded from clinical entry to 6 months after discharge [21] . A significant change in cholesterol levels was observed, reduction from 4.46 $\pm$ 0.90 mmol/ L on referral to 4.02 $\pm$ 0.72 mmol on discharge (p=0.002) [21].

Both studies suggest benefits of the clinic in improving medication regimens of the patients. These finding can be interpreted in terms of impact of reducing risk of CVD and the subsequent cost reduction of treating the CVD complications. However, there is a need to conduct rigorous evaluation of the clinic and compare outcomes to those achieved in patients who attend the clinic without referral to the pharmacist. No randomised controlled trials (RCT) have been conducted to demonstrate effectiveness of this complex intervention.

1.18 MRC framework and complex interventions

A complex intervention is a recognised term that can be applied to the health care offered by different healthcare practitioners who collaborate with each other. “It comprises a number of separate elements which seem essential to the proper functioning of the interventions although the 'active ingredient' of the intervention that is effective is difficult to specify. Complex interventions are built up from a number of components, which may act both independently and interdependently. The components usually include behaviours, parameters of behaviours (e.g. frequency, timing), and methods of organizing and delivering those behaviours (e.g. type(s) of practitioner, setting and location)”[23]

The pharmacist-led DCVR clinic can be considered as a complex intervention. If it was to be evaluated both the process in the clinic and the process experienced in the usual care would need to be defined to inform outcome measures and processes which could be applied in a prospective RCT. Before designing a full scale evaluation, a feasibility study needs to be conducted. This is required to define process and outcome measures for a definitive future RCT. The feasibility study will identify problems with recruitment, potential sample size and estimated difference in outcome measures. Feasibility studies help to overcome uncertainties associated with the method used in the full scale evaluation and makes the evaluation more reliable [24].

The full scale evaluation of the clinic not only can be used to measure outcomes of the clinic, but also can be used to fine tune an improved model of delivery of the complex intervention offered by the clinic. It also can lead to change in the organizational structure of the health care offered to diabetic patients [25].

1.19 Outcome measures

In order to evaluate the clinic, relevant and feasible outcome measures must be decided upon. A feasibility study was designed to retrospectively review data available for the pharmacist-led DCVR clinic and the usual clinic using data collected from the SCI-DC program and the notes written by the pharmacist upon the

consultations. The retrospective nature will not include patient interviews. Data collection will include the change in status of hypertension, dyslipidemia and blood sugar levels and changes in lifestyle habits of the patient [26]. Change in the pharmaceutical care plan will be assessed using the pharmacist notes and SCI-DC to find drug related problems and changes to patients' treatment in the clinic, including changes to the number of medication or dosage/ form. Patient admission, re-admission to the hospital and the length of hospitalisation will be recorded to assess if these are feasible outcome measures for a definitive trial. [27].

1.20 Advantages and disadvantages of prospective vs. retrospective study design

Prospective study usually take place over a long period of time, where the population included in the study is well defined and the population in general have a common characteristic. This kind of study design can be used to establish causality between the variables observed and the results obtained.

To use prospective study design to evaluate the clinic, outcome measures must be assigned before undertaking the study. The inclusion criteria must be decided prior to study start and then the population is divided into intervention group (patients managed in the pharmacist-led DCVR clinic) and a control group (patients managed in the normal clinic) Pre-assigning inclusion criteria and measurable outcomes can reduce sampling bias, design bias and selection bias [28].
The time required to accomplish prospective study can be disadvantageous. In the feasibility study we decided to study data from patients who had attended the clinic for at least 12 months and then followed them up for three years after discharge from the clinic in order to compare hospitalisation rate with patients in the comparative arm. Comparison of outcomes will inform sample size calculations and period of follow up required for a definitive prospective trial. The sample size and duration of follow up will inform the design and the costing for a research grant proposal.

Retrospective study design has limitations in terms of matching patients to inclusion criteria, potential for sampling bias, reliance on accurate documentation and completeness of data and the need to retrospectively 'clean' data. This design can be

more economic as large numbers of patients' records can be examined in a short period of time [28].

We decided to use retrospective design in a feasibility study to assess if the data currently collected routinely in practice could be used for evaluation in a future study. As this data already existed it was also feasible in a short period of time, to examine data over a period of time estimated to provide measures of outcome and potential differences in outcomes which could be used to power a future study.

2. Aim

2.1 To define outcome measures and the feasibility of data collection to inform a future RCT prospective study to evaluate the pharmacist-led DCVR clinic.

2.2 To define the size of effect of the pharmacist-led DCVR on outcome measures such as proportion of patients reaching BP target, proportion of quality standards reached for prescribing and hospital admission after discharge from the clinic to inform future power calculations.

2.3 To explore the feasibility of including economic evaluation.

3. Objectives

3.1 To characterise the diabetic population managed in NHS Lothian to include those who attend the secondary care diabetes clinics and those who attend or are eligible to attend to the pharmacist-led DCVR clinic

3.2 To compare outcome measures between patients eligible to attend the pharmacist-led DCVR clinic whom attend the secondary care diabetes clinic and patients who attend the pharmacist-led DCVR clinic in terms of admission rates after discharge from clinic, reasons for admission, length of hospitalisation, proportion meeting target BP, time to achieve target BP, lipid targets and drug related problems (DRP) to inform future evaluation. To correlate with pharmaceutical care issues outcome measures between the two groups will be compared to explore the feasibility of future evaluation including economic evaluation.

3.3 To compare time to dialysis, changes in albuminuria and BP in the subgroup of patients who attend the renal diabetic clinic between those who are referred to the pharmacist and those who are managed by usual care (secondary care diabetes clinic).

4. Subjects and settings

4.1 Research approval

The scientific officer of the South East Scotland Research Ethics services confirmed the study did not require research ethics approval (Appendix 3). The study was approved by the Pharmacy Quality Improvement Team. The investigator was an ERASMUS exchange student from the University of Tromsø whom had an honorary contract with NHS Lothian.

4.2 Settings

The study was undertaken at the Western General Hospital (WGH), Edinburgh. The design of the spreadsheet for data collection was performed at the Education, Research & Development department in collaboration with an administrator linked to the supervisory team.
The process of data collection took place partially at the diabetes unit, but mostly at the medical record office.

4.3 Subjects inclusion and exclusion

Patients were recruited retrospectively from the WGH. Patients attended the pharmacist-led DCVR clinic represented the intervention group. Patients managed by the diabetes clinic represented the control group.

The diabetes clinic offers approximately 3000 appointment per annum to diabetes patients. GP refer patients to the diabetes clinic to be managed by doctors to initiate or to optimise diabetes treatment and/or associated cardiovascular risk. Patients are offered up to three appointments every year depending on the rate of progression of DM and CVD. The doctor at the clinic recommends a treatment plan and the GP follows this plan in primary care. Approximately 60 patients are referred to the pharmacist-led DCVR per annum. The pharmacist focuses on management of cardiovascular risk factors. The clinic operates once a week and patients are offered a

review once every 6-8 weeks. Recommendations to change cardiovascular treatment are sent to the GP to commence changes in the primary care using the same process as letters from doctors.

Using SCI-DC a list of all patients who attended the clinic in 2007 whom had either hypertension, microalbuminuria or both were identified. Patients who were eligible to attend the pharmacist-led DCVR clinic and were not referred were included. Deceased patients, non-attendees and patients who had relocated were excluded as data was not available. Patients were also excluded if they had clear reasons for unstable BP, for example those who were pregnant, breast feeding or who had white coat hypertension. Patients who were attending both the pharmacist-led DCVR clinic and the usual clinic or renal clinic for management of cardiovascular risk factors were also excluded.

The initial proposal to include patients who had attended the clinic for 12 months was changed to 4 months as patients were seen a number of times within this time-frame and some patients were discharged from the clinic within 12 months. To allow enough time for hospital admission/re-admission it was proposed to collect data for patients who had been discharged from the clinic before 2009 providing a follow up period of 3 years. It was discovered that most patients attending usual care are not discharged despite being stable and at target physiological parameters; they continue to receive appointments varying between once or twice each year. Patients attending the pharmacist-led DCVR clinic are discharged after two consecutive visits with BP on target. Data from those in the usual care group was recorded up to three years from the first episode of cardiovascular risk.

Recruitment was initially modified to ease evaluation of guideline adherence. Treatment protocols had been updated in 2005 and in 2010. Patients were therefore recruited from those who had been referred to the clinic after 2005 and discharged before 2009. Following exclusion of patients as described above, numbers of eligible patients were inadequate and it was decided to include patients referred to the clinic in 2003-4 as differences in the treatment protocols 2003 and 2005 were minor. The time-period was used to recruit eligible patients for the usual care group. SCI-DC database could not perform a search to identify usual patients that fit the time parameter for the

inclusion criteria nor referral eligibility due to cardiovascular risk. Instead a list of all patients who attended the usual care in 2007 was generated (3300 patients), but was not purposeful; not all patients were eligible to be referred to the pharmacist-led DCVR clinic and the list did not include dates of referral and discharge from the clinic. A list of patients using cardiovascular medications was generated from the 2007 patients list, but the list did not include patients who had hypertension but were not treated. It was decided to generate three lists that included all the patients eligible to be referred to the pharmacist-led clinic; the first list included patients who had hypertension in 2007(BP>130/80mmHg), patients who had microalbuminuria in 2007(Albumin/Creatinine Ratio (ACR) >3.5 mg/mmol) and patients who had both hypertension and microalbuminuria in 2007. Patients who had two or more consecutive episodes of hypertension and/or microalbuminurea were identified. Patients treated at the pharmacist-led DCVR clinic, deceased patients, patients relocated, transferred to another hospital and non-attendees were identified using SCI-DC database and excluded. A list of patients who match the inclusion criteria was generated and randomised.

In total 45 patients from the pharmacist-led DCVR clinic were included (intervention) and 42 patients from the secondary care diabetes clinic were included (usual care).

5. Methods

5.1.1 Patients who attended the pharmacist-led DCVR clinic were recruited retrospectively; a list of patients discharged from the clinic before 2009 was supplied by the pharmacist.

5.2.2 It was anticipated that data could be retrieved from the SCI-DC database and the pharmacist's records. Data was incomplete therefore it was decided to undertake case note review using paper medical records. The investigator was granted access to the WGH medical records office in order to collect medical data. The pharmacist's notes were excluded as a source of data collection as the medical records contain more substantial information and are easier to interpret compared to the pharmacist's notes.

5.1.2 Data collection documents were allocated an identification number linked to a list of patient names and date of birth to make it possible to collect additional patient information if required at a later period. The list of patient names was kept in a locked filing cabinet within the Education, Research and Development department within the pharmacy department at the WGH. No patient identifiers were required for analysis. Anonymised data was transferred onto a password accessed Microsoft Access database. The database was designed to enable collecting data about demographics of patients (age, sex, duration and type of diabetes etc.), clinical parameters (BP, lipid values and kidney function status), drug history, medication related problems (MRP), guideline adherence and hospital admissions. The data base was tested by collecting information from 3 patients and was modified accordingly to enable gathering appropriate information and minimise time consumed to gather information.

5.1.3 Using SCI-DC and the medical record, the general demographics of the population of patients who attend the secondary care clinic who are eligible to attend the pharmacist-led DCVR clinic and the population of patients who attended the pharmacist-led DCVR clinic were recorded in a spread sheet developed by the investigator and the administrator linked to the supervisory

team. The demographics included: age, sex, type, duration and method of control of diabetes, co-morbidities, smoking habits, exercise habits and alcohol consumption on referral and when discharged. The demographics were compared between the two groups.

5.2.1 A literature search was performed to determine the most common outcome measures investigated when evaluating similar complex interventions. MeSH term in search engine Pubmed was used to search for studies containing the following key terms: pharmacist clinic AND diabetes, pharmacist clinic AND cardiovascular disease, diabetes AND cardiovascular disease, diabetes AND hospital admission, cardiovascular disease AND hospital admissions. Pubmed, Embase, Medline and Google were used to search for articles containing the following terms: diabetes outcomes, cardiovascular outcomes, diabetes hospitalisation and cardiovascular hospitalisation.

5.2.3 The investigator and the supervisors agreed on three classes of outcome measures: changes in physiological parameters changes in pharmaceutical care plan and impact of clinic on hospital readmissions. Changes in physiological parameters include change in BP between referral and discharge, change in lipid profile (total cholesterol, triglycerides, HDL-cholesterol) between referral and discharge and change in kidney functions (creatinine, ACR and urea) between referral and discharge. Change in pharmaceutical care plan was subcategorised into 8 classes of drug therapy problems using the definition established by Cipolle and Strand ; Unnecessary drug therapy, Additional drug therapy, Ineffective drug, Dosage too low, Adverse drug reaction, Dosage too high, Inappropriate compliance and Unclassified [2]. Guideline adherence was compared between the two clinics. Any deviation from the guidelines and the reason for non-adherence was recorded. Non-guideline adherence was subcategorised into four classes; choice, drug, unknown and non-applicable. Choice covers the deviation in dose, frequency and form of the medication. Drug covers the deviation in the type and class of medication. Unknown covers the deviation from guidelines without any justifiable reasons. Non-applicable covers the deviations when guidelines cannot be applied to certain situations.

Time to first hospital admission, number of subsequent admissions, length of hospitalisation and reason for admission are recorded and compared between the two clinics.

Mean and SD will be calculated for the different parameters, if not appropriate percentages and proportions will be calculated instead.

To demonstrate statistical difference, p value will be calculated, depending on the type of data, z-test, t-test and χ^2-test will be used accordingly to calculate the p-value.

5.3.1 The investigator was not granted access to the medical files of the patients experiencing care at the renal clinic. The subgroup of patients who attended the renal clinic was excluded from the study. The renal clinic was established recently which does not fit the time parameter in the inclusion criteria for collecting data about hospital re-admissions.

6. Results

6.1 Characterisation of diabetes population managed in NHS Lothian

A total of 87 patients were included in the study, 45 patients experienced health care at the pharmacist-led DCVR clinic (intervention group) and 42 patients were treated in the usual care (control group).

Most patients in both groups had type 2 DM. Patients in the intervention group were significantly older than those in the control group and had a longer duration of diabetes. A greater proportion of patients in the intervention group used insulin.

The baseline physiological values were collected from the first appointment at the clinics. Baseline SBP, ACR and total cholesterol did not present significant difference between the groups (p=0.25, p=0.30, p=0.22). The baseline DBP and HbA1c presented a significant difference (p= 0.0003 and p=0.026). The intervention groups had a significantly greater number of cardiovascular medications on referral (p<0.001) and a greater mean of comorbidities per patient (p=0.022) Patient demographics are described in table 1.

Table 1: General demographics of the intervention and the control group at baseline

Characteristics	**Intervention**	**control**	**p-value**
Number of patients	45	42	
Mean age (SD) years	64.58 (10.29)	56.69 (11.12)	0.0006 (z-test)
Males	22 (48.89%)	24 (57.14 %)	
Weight (Kg)	93.33	88.05	0.26 (z-test)
BMI	34.47	31.90	0.11 (z-test)
Type 2 DM	44 (97.78%)	37 (88.10%)	
Type 1 DM	1 (2.22%)	5 (11.90%)	
Duration of disease (Months)	104.28	30.81	0.003 (z-test)
Diabetes method of control			
Diet	5 (11.11%)	4 (9.52%)	
Tablets	24 (53.33%)	29 (69.05%)	
Insulin only	9 (20.00%)	7 (16.67%)	
Insulin & Tablets	7 (15.56%)	2 (4.76%)	
Smoking status			
Smoker	10 (22.22%)	12 (28.57%)	
Ex-smoker	7 (15.56%)	7 (16.67%)	
Never smoked	26 (57.78%)	21 (50.00%)	

Table 1 continued

Characteristics	Intervention	control	p-value
Unknown	2 (4.44%)	2 (4.76%)	
Alcohol consumption			
Excess limit	4 (8.88%)	4 (9.52%)	
Within limit	15 (33.33%)	11 (26.19%)	
Non-drinker	11 (24.44%)	3 (7.14%)	
Unknown	15 (33.33%)	24 (57.14%)	
Activity status			
Slight active	15 (33.33%)	3 (7.14%)	
Inactive	16 (35.56%)	2 (4.76%)	
Unknown	11 (24.44%)	36 (85.71%)	
Blood pressure			
Mean SBP (SD) mmHg	155.09 (19.02) (n= 45)	150.85 (15.31) (n=41)	0.25 (z-test)
Mean DBP (SD) mmHg	80.38 (10.31) (n= 45)	88.32 (10.01) (n=41)	0.0003 (z-test)
Total Cholesterol	4.57 (0.95) (n=27)	4.88 (1.10) (n=36)	0.22 (t-test)
ACR (mg/mmol)	22.5 (47.80) (n=22)	11.62 (14.35) (n=29)	0.30 (t-test)
HbA1c	7.92 (1.46) (n=17)	9.03 (2.09) (n=41)	0.026 (t-test)
Mean number of cardiovascular Medications on referral	4.53 (1.69)	1.54 (1.64)	<0.0001 (z-test)
Co-morbidities			
Hypertension	41 (91.11%)	40 (95.24%)	
PVD	4 (8.88%)	0 (0%)	
Angina	5 (11.11%)	1 (2.38%)	
IHD	9 (20.00%)	1 (2.38%)	
MI	2 (4.44%)	1 (2.38%)	
CABG	2 (4.44%)	2 (4.76%)	
Stroke/TIA	3 (6.67%)	1 (2.38%)	
Hyperlipidemia	15 (33.33%)	20 (47.62%)	
Heart failure	0 (0%)	1 (2.38%)	
Microalbuminurea	17 (37.78%)	19 (45.24%)	
Nephropathy	10 (22.22%)	4 (9.52%)	
Retinopathy	7 (15.56%)	1 (2.38%)	
Neuropathy	8 (17.78%)	1 (2.38%)	
Mean number comorbidities per patient	2.74 (1.36)	2.19(0.83)	0.022 (z-test)
Total number of comorbidities	123	92	

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; ACR, Albumincreatinine ratio; PVD, Peripheral Vascular disease; IHD, Ischemic heart disease; MI, Myocardial infarction; CABG, Coronary artery bypass graft; TIA, Transient ischemic attack.

6.2 Comparison of outcome measures between the intervention group and the control group

The BP target to evaluate the number of patients reaching BP target were taken from the treatment protocol used in the pharmacist-led DCVR clinic:

- Type 1 and 2 diabetics with no microalbuminurea- target < 140/80 mmHg
- Type 1 diabetics with nephropathy - target < 120/70 mmHg
- Type 2 diabetics with microalbuminurea – target < 135 / 75 mmHg

The reduction of SBP was significantly greater in the intervention group, 19.18mmHg (p=0.0088) and a greater proportion of patients reached the target BP in the intervention group (57.78%) than in the control group (26.83%) (p=0.0038). The difference in reduction of DBP, total cholesterol and ACR was not significant between the two groups. The change in physiological parameter is summarised in table 2.

Table 2: change in Blood pressure, Albumincreatinine ratio and Total cholesterol

Characteristics	**Intervention**		**control**		**P-value**
Change in SBP (mmHg)	Mean	-19.18	Mean	-8.34	0.0088
	SD	19.86	SD	18.56	(z-test)
	SE	2.96	SE	2.90	
	n	45	n	41	
Change in DBP (mmHg)	Mean	-9.36	Mean	-6.78	0.28
	SD	9.7	SD	11.97	(z-test)
	SE	1.45	SE	1.87	
	n	45	n	41	
Number of patient reaching target BP (%)	26 (57.78)		11 (26.83%)		0.0038 (χ^2-test)
Change in ACR	Mean	- 2.89	Mean	-5.47	0.68
	SD	29.27	SD	14.13	(t-test)
	SE	6.24	SE	2.62	
	n	22		29	
Change in Cholesterol	Mean	-0.14	Mean	-0.69	0.52
	SD	0.76	SD	1.12	(t-test)
	SE	0.15	SE	0.20	
	n	27	n	35	
Change in HbA1c	Mean	-0.04	Mean	-1.72	0.0013
	SD	1.14	SD	2.33	(t-test)
	SE	0.34	SE	0.36	
	n	17	n	41	

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; ACR, Albumincreatinine ratio; SD, standard deviation; SE, standard error; n, sample size.

The pharmacist made a significant number of changes to the pharmaceutical care plan. In total starting 46 new antihypertensive therapies and increasing the dose of 30

antihypertensive therapies to the maximum recommended dose. The usual care started 27 antihypertensive therapies and increased the dose of 12 antihypertensive therapies to the maximum recommended dose. A summary of all subclasses of antihypertensive therapies, antiplatelet therapy and lipid lowering therapy initiated and doses increased is summarised in table 3.

Table 3: Change in pharmaceutical plan

Medication	**intervention**	**control**
ACE-inhibitors		
Started	5	16
Dose increased	19	11
Dose increased to ≥ 100% of recommended dose	8	6
ARB		
Started	5	2
Dose increased	8	5
Dose increased to ≥ 100% of recommended dose	6	3
Calcium channel blocker		
Started	8	3
Dose increased	12	1
Dose increased to ≥ 100% of recommended dose	9	1
Started Thiazide	4	3
Frusemide		
Started	5	1
Dose increased	4	1
Dose increased to ≥ 100% of recommended dose	4	1
Started β-blocker	5	2
α-blocker		
Started	9	0
Dose increased	15	0
Dose increased to ≥ 100% of recommended dose	2	0
Spironolactone		
Started	5	0
Dose increased	8	0
Dose increased to ≥ 100% of recommended dose	2	0
ACE-inhibitor started or increased	24	27
ARB started or increased	13	7
Calcium channel blocker started or increased	20	4

Table 3 continued

Medication	intervention	control
Thiazide started or increased	4	3
Frusemide started or increased	9	2
β-blocker started or increased	5	2
α-blocker started or increased	24	0
Spironolactone started or increased	13	0
Total	112	45 ($p<0.001$) (χ^2-test)
Total number of antihypertensive increased to ≥ 100% of recommended dose	30	12
Started Aspirin	5	10
Started Clopidogrel	10	0
Statin Started	10	23
Statin dose increased	9	4
Statin dose increased to ≥ 100% of recommended dose	6	2

ACE-inhibitors, Angiotensin Converting Enzyme inhibitor; ARB, Angiotensin Receptor blocker

The total number of MRP documented in the intervention group were twice as much the number of MRP documented in the control group (p=0.0058). The most prominent MRPs documented were the need to add a drug therapy (71 problems in intervention group and 60 in the control group) and the need to increase doses (75 problems in the intervention group and 21 in the control group). The pharmacist documented detection of 3 unnecessary drug therapies, 3 medications above recommended dose and 14 adverse drug reactions constituting more than 10% of all MRPs. The usual care failed to document detection of any unnecessary drug therapy or very high doses and only managed to document detection of 3 adverse drug reactions. The classification and the count of the different MRPs is summarised in table 4.

Table 4: Medication related problems actioned

Medication	Intervention (n=45)	control (n=42)	p-value
Type of drug therapy problem			
Unnecessary drug therapy	3 (1.67%)	0 (0%)	
Additional drug therapy	71 (39.44%)	60 (66.67%)	
Inappropriate drug	11 (6.11%)	5 (5.56%)	
Dose too low	75 (41.67%)	21(23.33%)	

Table 4 continued

Medication	Intervention (n=45)	control (n=42)	P-value
Dose too high	3 (1.67%)	0 (0%)	
Adverse drug reaction	14 (7.78%)	3 (3.33%)	
Inappropriate compliance	3 (1.67%)	1 (1.11%)	
Unclassified	0 (0%)	0 (0%)	
Total number of MRP	180	90	0.0058 (χ^2-test)
Mean MRP per patient	4.19	2.81	0.017 (z-test)

MRP, medication related problem

The treatment protocol used in the pharmacist-led DVCR clinic is based on the Scottish Intercollegiate Guidelines Network (SIGN) guidelines and developed in cooperation with doctors in the usual care indicates subclasses and generic names of antihypertensive medication and stating clearly the starting dose, maintenance dose and maximum dose for every medication in each of the 5 steps of the treatment stages. The 4-steps treatment protocol adapted by the usual care, is based on the SIGN guideline and the British National Formulary (BNF), states only the subclasses of antihypertensive therapy to be used without indicating a certain generic name or dose.

Table 5: Guideline adherence

Guideline	Intervention	control group
Antihypertensive		
Step 1	22	22
Step 2	17	15
Step 3	13	4
Step 4	10	1
Step 5	14	-
Antiplatelet therapy adherence	37	11
Lipid lowering therapy adherence	25	12

The prescribing quality of statins and antiplatelet therapy in the usual care and the pharmacist-led DCVR clinic varied. The reasons for guideline non-adherence in the pharmacist clinic were clearly documented; the type of drug and the dosage choice were the most eminent reasons for guideline non-adherence. The reasons for guideline non-adherence in the usual care were less well documented, leading to “unknown

reasons" being the major reason for guideline non-adherence. Table 6 summarises the guideline non-adherence for platelet and Statin therapy.

Table 6: Guideline non-adherence lipid lowering therapy and antiplatelet therapy

Guideline	**Intervention**	**control group**
Antiplatelet		
Drug	4	0
Choice	1	3
Unknown	0	9
Non-applicable	3	5
Total	8	17
Lipid lowering therapy		
Drug	5	3
Choice	13	8
Unknown	2	19
Non-applicable	0	1
Total	20	32

Four patients from the intervention group were admitted to the hospital after discharge from the clinic, the total number of admissions was 6. Only one patient from the control group was admitted to the hospital after the last appointment in the usual care, the total number of admissions for that patient was 3. The reason for admission was unable to be obtained, but the speciality the patients were admitted to was able to be obtained. The length of hospitalisation was unable to be obtained. Table 7 summarises the admission data for the two populations.

Table 7: Cardiology and vascular hospital admissions

	Intervention	**control group**
Number of patients admitted to the hospital	4	1
time to first admission (months)	14	10
total number of admissions	6	3

6.3 Comparisons of outcome measures between renal diabetic patients and usual care.

As stated in the method, the investigator was not granted access to the medical files of the patients experiencing care at the renal clinic. The subgroup of patients who attended the renal clinic was excluded from the study. The renal clinic was established

recently which does not fit the time parameter in the inclusion criteria for collecting data about hospital re-admissions.

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Calculation of future study subjects size

1) Calculation based on proportion of patients reaching target BP

a) Power = 80% significance (p<5%)

$$n= \frac{8[x(1-x)+y(1-y)]}{(x-y)^2}$$

n= number of subjects per group

x= proportion in group 1
y= proportion in group 2

$$n= \frac{8[0.27(1-0.27)+0.58(1-0.58)]}{(0.27-0.58)^2} = \underline{36.69 \approx 37 \text{ patients in each groups}}$$

b) Power = 90% significance (p<5%)

$$n= \frac{11[x(1-x)+y(1-y)]}{(x-y)^2}$$

n= number of subjects per group

x= proportion in group 1
y= proportion in group 2

$$n= \frac{11[0.27(1-0.27)+0.58(1-0.58)]}{(0.27-0.58)^2} = \underline{50.44 \approx 50 \text{ patients in each group}}$$

2) calculation based on SBP means

a) Power= 80% significance (p<5%)

$$n= \frac{16 \times SD^2}{(X-Y)^2}$$

n= number required per group

SD = Standard Deviation
X= mean of group 1
Y= mean of group 2

$$n= \frac{16 \times 18.56^2}{(8.34-19.18)^2} = \underline{46.9 \approx 47 \text{ patients in each group}}$$

b) Power= 90% significance (p<5%)

$$n=\frac{21\times SD^2}{(X-Y)^2}$$

n= number required per group

SD = Standard Deviation
X= mean of group 1
Y= mean of group 2

$$n=\frac{21\times 18.56^2}{(8.34-19.18)^2} = \underline{61.56 \approx 62 \text{ patients in each group}}$$

3) calculation based on DBP

a) Power= 80% significance (p<5%)

$$n=\frac{16\times SD^2}{(X-Y)^2}$$

n= number required per group

SD = Standard Deviation
X= mean of group 1
Y= mean of group 2

$$n=\frac{16\times 11.97^2}{(9.36-6.78)^2} = \underline{344.4 \approx 344 \text{ patients in each group}}$$

b) Power= 90% significance (p<5%)

$$n=\frac{21\times SD^2}{(X-Y)^2}$$

n= number required per group

SD = Standard Deviation
X= mean of group 1
Y= mean of group 2

$$n=\frac{21\times 11.97^2}{(9.36-6.78)^2} = \underline{452.03 \approx 452 \text{ patients in each group}}$$

Case study:

A random patient was chosen from the pharmacist-led DCVR clinic and the usual care, the change in the SBP is plotted against the number of visits. The change in medical therapy is demonstrated under each appointment.

Figure 1: SBP vs. no. of visits for a random patient receiving treatment at the pharmacist-led clinic

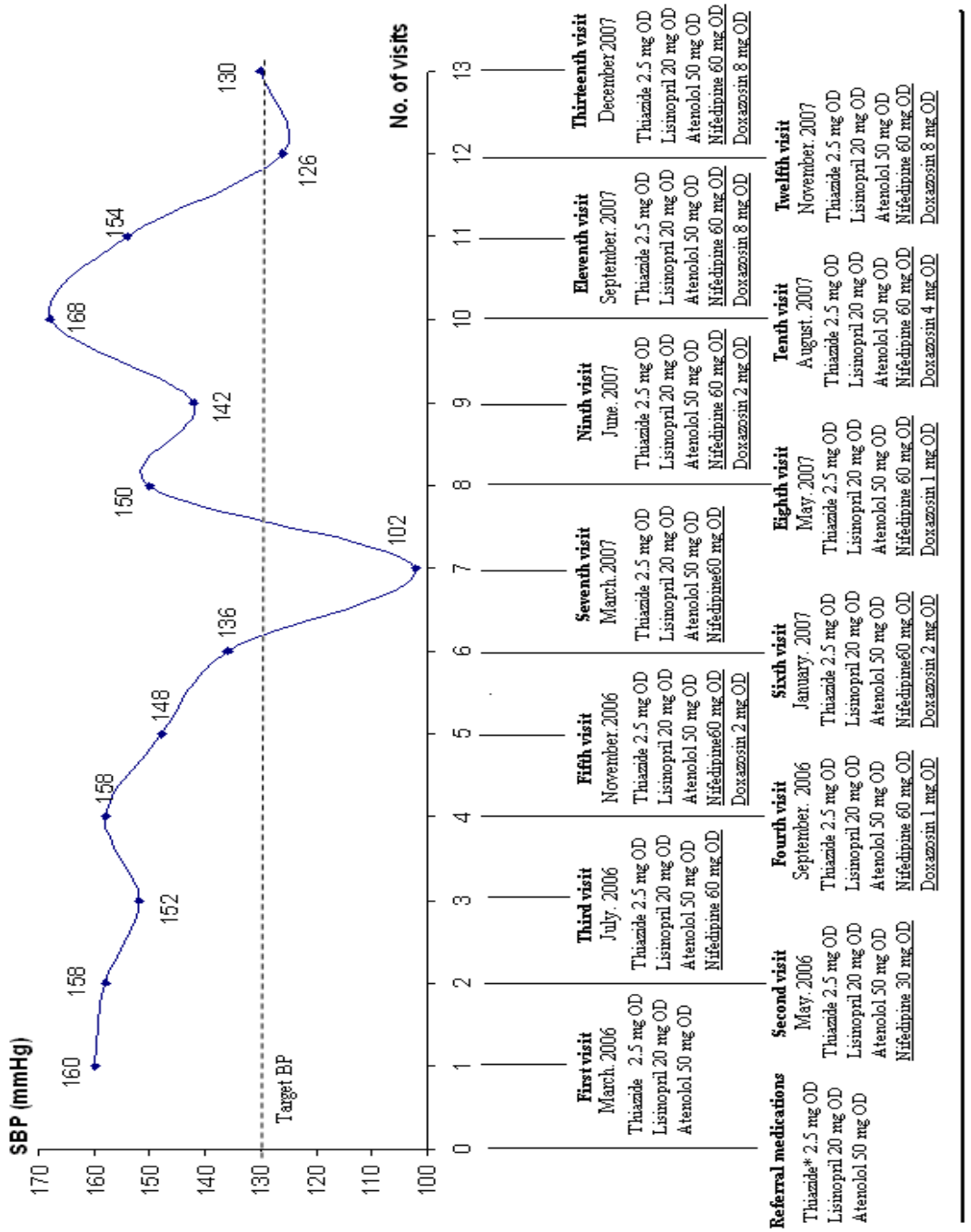
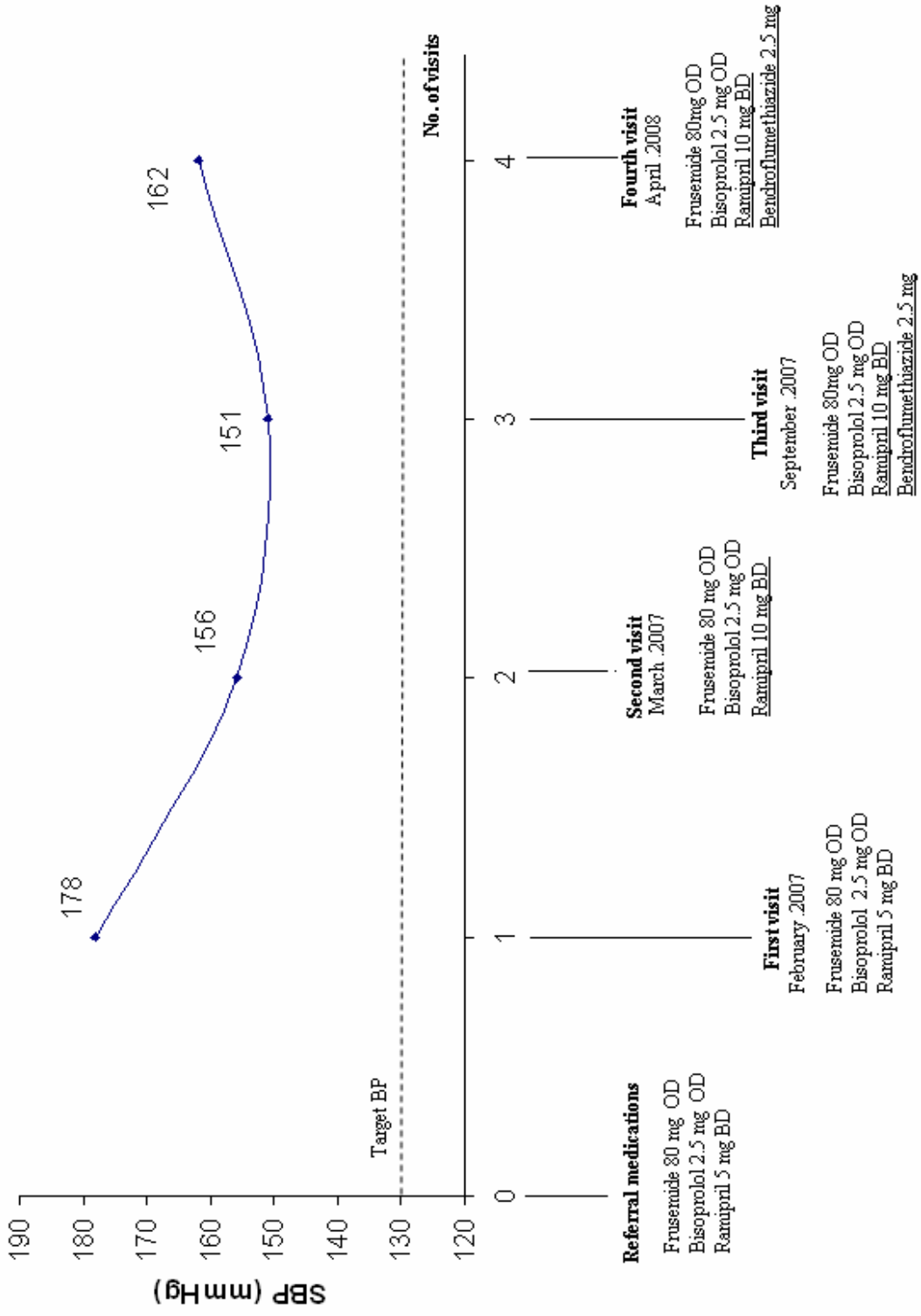


Figure 2: SBP vs. no. of visits for a random patient receiving treatment at the usual care.



7. Discussion

7.1 Principal findings

The study aimed to evaluate the feasibility of outcome measures and demonstrate differences, favouring the intervention offered by the pharmacist-led DCVR clinic over the usual care carried out by doctors in changes in physiological parameters, changes in pharmaceutical care plan and MRP for patients with diabetes attending hospital outpatient clinic at the WGH.

7.1.1 Characterisation of diabetes population managed in NHS Lothian

The intention was to recruit a control from those patients eligible to attend the pharmacist-led DCVR clinic. A lack of clearly defined parameters led to use kidney impairment measured in ACR and hypertension as risk factors to define the control group. These risk factors are used as referral criteria in the pharmacist-led DCVR clinic referral form.

There was no statistical difference documented between the intervention and the control group in baseline BP, ACR and cholesterol, however significant differences were detected in other characteristics. Patients in the intervention group were significantly older, had a longer duration of diabetes, a greater number of comorbidities, and a more significantly greater number of cardiovascular medications on referral. There might be a trend of more patients using insulin in the intervention group than patients in the control group. These differences indicate the significantly higher cardiovascular risk in the intervention group, influence the impact of the pharmacist-led DCVR clinic on cardiovascular risk reduction and complicate the process of feasibility evaluation of outcome measures. These variations question the validity of using the established referral criteria and how often they are being used. Other local work carried out by a student colleague from the University of Tromsø documented the detection of the referral of approximately 5% of eligible patients to the pharmacist–led DCVR clinic. It seems there were other factors that predicted referral than the ones established in the referral form.

It is proposed that subjects in the future study will be recruited prospectively and randomised into an intervention and a control group to eliminate variations and inconsistencies between the groups in terms of baseline characteristics and inclusion criteria will have to be clearly defined.

7.1.2 Feasibility of outcome measures in the intervention and the control group

Patients in the intervention group were referred to the pharmacist-led DCVR clinic with a greater number of cardiovascular medication and greater cardiovascular risk than the control group. However, they had a greater mean reduction of SBP and a greater proportion of patients reached the target BP set by the guidelines. These changes represented a statistical significance and could be considered as feasible outcome measures which can be used as primary end points to calculate the future prospective population size. The mean reduction in DBP was greater in the intervention group but was not statistically significant. Time elapsed to reach target BP between the two groups could not be compared due to the differences in the model of intervention delivery. The pharmacist-led DCVR clinic specialises in reducing cardiovascular risk, offers frequent follow up and patients are discharged after they reach treatment target. The usual care specialises in diabetes treatment but is not a specific cardiovascular clinic, can not offer frequent follow up and only a small proportion of patients were discharged. The time elapsed to reach target BP could be recorded in the prospective study and used for analysis.

The study did not detect significant difference in ACR reduction between the intervention and the control group. The ACR calculations were based on a proportion of the patients in both groups, as unreliable and incomplete data had to be excluded. It was anticipated that the ACR would be significantly reduced in the intervention group as the degree of kidney impairment is closely related to the hypertension status. However, the number of patients with nephropathy was greater in the intervention group. Patients in the control group were referred to the usual care to initiate or optimise diabetes treatment, the HbA1c reduction was significantly different between the control group and the intervention group as the pharmacist-led DCVR clinic

specialises in cardiovascular risk only and does not recommend changes to the diabetes management. A trend was detected in reduction of ACR following the reduction of HbA1c in the control group and might attribute to the insignificant difference in ACR reduction between the control group and the intervention group. This finding is in concordance with a previous study conducted to evaluate the relationship between HbA1c and microvascular complications, which concluded there is a linear correlation between HbA1c and ACR and microvascular complications[30]. The study concluded change in ACR is an unfeasible outcome measure due to insignificant reduction in ACR between the intervention and the control group, however reduction in ACR could be used as a marker for reduced cardiovascular risk in the future study if both populations would have a comparable comorbidities profile (ACR, microalbuminurea and nephropathy). Also choosing groups with similar baseline HbA1c and duration of diabetes would eliminate the confounding effect the HbA1c has on ACR and microvascular disease. It is essential to record values accordingly to produce comparable data in both groups.

The study documented a greater degree of reduction in total cholesterol in the control group, but did not represent a significant statistical difference. Total cholesterol calculations were based on a proportion of the population groups, incomplete and unreliable data had to be excluded. Most patients referred to the pharmacist-led DCVR clinic were prescribed statins prior to referral and were referred to the clinic to optimise treatment, while most patients referred to the usual care were not prescribed statins prior to referral and the lipid lowering treatment was initiated at the clinic. The difference in referral stage might explain the insignificant difference in total cholesterol reduction. The lipid lowering therapy protocol is a simple two steps protocol that could be carried out without the need to titrate the doses frequently, which fits into the model of care delivery offered by the usual care.
Changes in the treatment protocol of the usual care came about to include the recommendation of Statin therapy to all type 2 diabetics in the year 2005, which might explain the number of patients who were referred to the pharmacist-led DCVR clinic without being prescribed statin therapy.
A trend was observed in the control group in terms of reduction in HbA1c followed by a reduction in total cholesterol. The reduction of HbA1c and the initiation of statin therapy to in the control group can explain the differences in reduction of total

cholesterol between the two groups. The correlation between reduced HbA1c and reduction in total cholesterol was in concordance with previous studies conducted to evaluate the effect of glycaemic control on lipid profiles[31].

The study concluded change in total cholesterol was unfeasible outcome measure; the change in cholesterol in the future study might not be an indicator on the impact of the clinic to reduce cardiovascular risk.

Most medication changes were recorded in the letters to the GP, which is considered as a reliable source of changes in the pharmaceutical care plan. The changes recommended by the pharmacist led to a significant increase in the number of antihypertensive treatment and increased the dose of the medications in the intervention group more than changes recommended by the doctors in the control group.

These changes might explain the significant reduction in BP and the significant proportion of patients in the intervention group reaching target BP. There were some prominent differences in the antihypertensive treatment changes between the groups, the medications in the last steps of the treatment protocol for the pharmacist-led DCVR clinic (Spironolactone and α-blockers) were not prescribed by the doctors in the usual care, despite the collaboration between the pharmacist and usual care doctors to develop the treatment protocol for the pharmacist-led DCVR clinic. Changes in the number of antihypertensive medications between first and last appointment, differences in the doses increased and the numbers of medications increased to maximum dose could be a feasible outcome measure and could explain the changes in the physiological parameters.

The study documented the detection of a significantly greater number of MRP and a significantly greater mean of problems for each patient in the intervention group than the control group. The detection of these problems led to optimising the pharmaceutical care plan and might have reduced the risk for CVD in the intervention group. The model of treatment delivery through the frequent follow up (every 6 to 8 weeks) prompt by the achieved quality of prescribing and the well-defined guidelines used by the pharmacist-led DCVR clinic attributed to the differences observed in the changes in the pharmaceutical plan and the number of MRPs. This can also be used to describe the significant change in SBP and the significant number of patients reaching target BP. In contrast the infrequent follow up by the usual care and the vague

guidelines, which might have influenced the prescribing quality, explain the small change in BP, number of patients reaching BP target, pharmaceutical care plan and number of MRP actioned.

The uneven distribution of related comorbidities between the two groups renders the differences in cardiology and vascular hospital admission insignificant. The intervention group had more patients admitted and a greater number of hospital admissions. Data concerning the length of hospitalisation and the outcome of hospitalisation were not provided by the Lothian health intelligence unit. The study found hospital admissions not feasible as an outcome measure, however in the future study hospital admissions can be valuable in evaluating the clinic when adequate numbers of subject with similar comorbidities and characteristics are included. Comparison of hospital admissions is a vital part of the economic evaluation of the intervention.

7.2 strengths and limitations of the study

7.2.1 Difficulties in retrieving data

Using the diabetes database SCI-DC proved to be sub-optimal for data collection. SCI-DC database did not contain data on medication prescribed prior to first visit to the clinics and did not contain detailed documented physiological values. A more efficient way of collecting data was to access the patients' medical record stored in the WGH medical record office. It was time consuming to grant authorisation to access the medical records, also the process of data retrieving from the medical records proved to be time consuming. During the process of data collection it was discovered medical records were destroyed for patients who did not receive treatment in the hospital for the past six years. The destruction of medical files reduced the number of patients in the intervention and led to only including patients who continued to receive treatment at the hospital after discharge from the pharmacist-led DCVR clinic. Medical records of deceased patients were removed from the medical record office and stored in a separate office, which proved to be inaccessible as authorisation was not granted to access these records. Mortality can be considered as a

primary end point, the number of deceased patients post discharge, time to mortality after discharge and the reason for mortality could be subjected to comparison between the different clinics.

7.2.2 Identifying comparable populations

The differences in the model of care delivery and the differences in the setup of the pharmacist-led DCVR clinic and the usual care clinic led to unanticipated complications in selecting suitable patients for the study. The intervention group were selected from a list of patients discharged from the clinic before 2009 supplied by the clinic's pharmacist.

The diabetes database SCI-DC could not be used to generate a list of patients discharged before 2009 from the usual care. Most patients attending the usual care do not get discharged despite being stable and reaching target physiological parameters, patients are still followed up, but less frequently (once a year). The usual care is a specific clinic for treating diabetes and not specific for treating hypertension and reducing CVD risk, however hypertension is managed in the clinic, but it's not the main focus. The pharmacist-led DCVR clinic specialises in treating hypertension and reducing CVD risk.

Identifying patients from the usual care was difficult and time consuming. SCI-DC database was used to identify patients with minimum SBP of 140 mmHg and DBP of 80 mmHg and/or microalbuminurea (ACR >2.5 mg/mmol). However it could not be used to identify patients with similar comorbidities and duration of diabetes to the intervention group.

It was planned to compare patients over a similar period of time, but proved to be sub-optimal, intervention group patients were monitored every 6-8 weeks and most patients were discharged within a year of the first appointment. The control group were followed up once or twice per annum. This led to change the inclusion criteria to record appointments up to 36 months from the first appointment in the control group.

7.2.3 Evaluation of guideline adherence

The study design enabled data collection about guideline adherence, guideline non-adherence and reasons for guideline non-adherence, however failed to develop an advanced guideline adherence assessment tool; the stage of treatment initiated for patients using cardiovascular medication prior to referral and the chronological order of adhering to guidelines was not recorded. Thus no conclusion about the assessment of guideline adherence and the achieved prescribing quality can be drawn.

7.3 Comparisons to other studies

7.3.1 Reduction in BP and Cholesterol

Currently there are a limited number of studies published to evaluate the pharmacist-led DCVR clinic. This makes it difficult to compare the study conducted to others published in the same field.

In 2008 a study was conducted to evaluate the impact of the pharmacist-led DCVR clinic on cardiovascular risk which included 34 patients, documented a significant reduction in BP 23/10mmHg ($p<0.001$), AMBP reduction of 13/9 mmHg in BP and an increase in the number of antihypertensives from 2.82(±1.05) to 3.67(± 1.12). The study also documented a significant reduction in total cholesterol by 0.4mmol/L ($p=0.002$)[21], however the study did not include a control group. The change in BP, total cholesterol and number of antihypertensive medication was compared between the first and last visit for the intervention group only. Hence no conclusion can be drawn on the significant difference of impact of the pharmacist clinic compared with usual care. Our study documented 19/9 mmHg reduction in BP in the intervention group and 8/7 mmHg reduction in the control group. The reduction in total cholesterol was greater in the control group, 0.69 mmol/l for control group and 0.14 mmol/l for intervention group, but did not represent a statistical difference ($p=0.52$). A great proportion of patients in the control group were not prescribed statins prior to referral

which might explain the great reduction in total cholesterol in the control group. The control group also had a suboptimal diabetes control, hence reduction in HbA1c led to reduction in total cholesterol.

7.3.2 Impact on pharmaceutical care plan and hospital admissions

The pharmacist intervention was evaluated and compared to the usual care in a study conducted on patients with left ventricular systolic dysfunction. The study included 2614 patients with mild or moderate heart failure and evaluated the pharmacist's impact on the pharmaceutical care. The primary outcome was death from any cause or admission for heart failure, secondary outcome was death from any cause or admission for cardiovascular cause. The study detected an improvement in the use of disease modifying medication; a greater number of initiations and dose increases in ACE-inhibitors, ARB and β-blockers were detected in the intervention group, however failed to demonstrate a positive impact of the pharmacist intervention on heart failure mortality and number of admissions; 337 patients died from the intervention and 331 from the control group ($p=0.92$). The number of admissions for heart failure was 107 in the intervention group and 114 for the control group ($p=0.38$) and the total number of admissions for any reason was 711 in the control group and 695 in the control group ($p=0.730$)[32]. Our study has also demonstrated a significant difference in the number of cardiovascular medications initiated or increased ($p<0.001$) between the intervention and the control group, however there were more patients admitted from the intervention group and a greater number of total admissions. Patients in the intervention were significantly older, had longer duration of diabetes and had a greater number of comorbidities which explains the greater number admissions and number of patients admitted to the hospital.

7.4 Future considerations

7.4.1 Population size

The size of the intervention and the control group to be included in the future study was calculated based on the primary outcome measures in reduction of SBP, DBP and the number of patients in each group reaching BP target. Reduction in ACR and total cholesterol and the difference in hospital admission rates were not appropriate in calculating the future study size because a greater impact was recorded in the control group.

The change in SBP and the proportion of patients reaching BP target was statistically different between the intervention and the control group. Reduction of DBP was greater in the intervention group but was not significant between the two groups. The future study population size was calculated based on DBP, depending on the power of the study, if the power of the study is chosen to be 80% and $p<0.05$ then each group in the study must contain at least 344 patients. If 90% power was chosen with $p<0.05$ then at least 452 patients should be included. Recruiting this number of patients might be possible, but following up these patients will present a challenge for the pharmacist-led DCVR clinic. Collaboration between pharmacist-led DCVR clinics in Edinburgh might be required or probably considering smaller number might be more feasible.

7.4.2 Demographics of the study populations

In order to conduct a proper evaluation of the pharmacist intervention, control and intervention groups must be chosen with similar baseline characteristics in terms of physiological parameters, diabetes status and duration and comorbidities. The main co founder that effected the evaluation of pharmacist intervention impact on BP, ACR and total cholesterol was HbA1c. Choosing groups with similar baseline HbA1c would eliminate the variation caused by differences in HbA1c. The distribution of comorbidities between the groups must be even, patients with previous comorbidities

are more likely to be admitted to hospital and have a longer duration of hospitalisation. It is also important to collect admission details which include specific specialities and diagnostic codes. All admission and even non cardiology or vascular admission should be collected and related admissions should be included in the study.

The study did not manage to demonstrate a great impact of the pharmacist-led DCVR clinic in the ACR due to the greater number of patients with nephropathy, longer duration of diabetes and the change detected in HbA1c in the control group which led to reduction in ACR.
ACR is linearly correlated to BP, thus can reflect the effect of reduction of BP in the kidney function. There might be a need for subgroup analysis for patient with end stage renal failure (nephropathy). Patients can be divided into groups according to ACR; normal value (ACR 0-3.5 mg/mmol), microalbuminurea (ACR 3.5-35 mg/mmol) and nephropathy (ACR>35mg/mmol) to ensure even distribution and avoid incorrect assessment. Fifty percent reduction in ACR for patients with nephropathy and number of patients reaching target of ACR <3.5 mg/mmol can be considered at as outcome for the future study.

7.4.3 Economic evaluation

Economic evaluation must be conducted to estimate the effect of the pharmacist-led DCVRclinic on health expenditure. There are a limited number of papers published to estimate the cost effectiveness of the pharmacist led clinic. A study published in 2007 estimated risk reduction with 11.9% for Coronary heart disease and 9.6% for cerebrovascular accident cost per event avoided was 34,708 pounds and 63,320 pounds. However, the study contained a small number of subjects, lacked a control group and was conducted over a short period of time[33.]
Cost benefit (gain and lose analysis in monetary) and cost effectiveness (cost in monetary and effect in gain in health e.g. year gained) can be conducted to evaluate the clinic. Direct and indirect costs must be taken into account. The cost to see a physician is much greater than the cost to see a pharmacist; however the model of care delivery offered by the pharmacist dictates frequent follow up and monitoring by

the pharmacist. Other direct costs must be taken into account such as the cost of materials used and cost of hospital space. Indirect cost must also be considered due to reduced efficiency and absence from workplace.

The pharmacist intervention was shown to affect the pharmaceutical care plan by initiating cardiovascular medications or increasing the dose more than the usual care, these changes come at a price, although might be leading to reduce cardiovascular risk; these changes are more expensive than the changes performed by the physicians[34].

8. Conclusion

The study aimed to evaluate the feasibly of outcome measures between patients attending the pharmacist-led DCVR clinic and the usual care clinics led by physicians. The study documented significant differences in BP reduction, changes in pharmaceutical care plan and drug therapy problems actioned between the intervention and the control group.

Feasibility study is a valuable tool to pave the way for a future randomised study by evaluating feasible outcome measures and uncovering unexpected difficulties prior to conducting a bigger scale evolution.

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Appendices

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Appendix 1: treatment protocols for the pharmacist-led clinic

a) Treatment protocol for the year 2003

DIABETES CARDIOVASCULAR RISK MANAGEMENT CLINIC
TREATMENT GUIDELINES

1. TREATMENT OF HYPERTENSION

Goal of therapy:
To achieve the following BP targets:

Type 1 and 2 diabetics with no microalbuminuria – target < 140/80mmHg
Type 1 diabetics with nephropathy – target < 120/70mmHg
Type 2 diabetics with microalbuminuria – target < 135/75mmHg

(i)Without macrovascular disease

Initiation of treatment

Medicine/initial dose	Maintenance dose	Positive indications	Contra-indications
Bendrofluazide 2.5mg daily*	Bendrofluazide 2.5mg daily*	elderly	Gout,moderate renal failure
Atenolol 50mg daily*	Atenolol 50mg daily*	CHD	Asthma,heart block
Ramipril 1.25mg daily	Ramipril 2.5-5mg daily	LVSD/diabetic nephropathy	Renovascular disease
Amlodipine 5mg daily	Amlodipine 10mg daily	ISH	Unstable angina
Doxazosin 1mg daily**	Doxazosin 4mg daily(maximum 16mg daily)	Prostatism	Urinary incontinence
Losartan 50mg daily**	Losartan 100mg daily	ACEI-cough/LVH	Renovascular disease
Irbesartan 150mg daily**	Irbesartan 300mg daily	Renal disease	Renovascular disease

*ceiling doses for antihypertensive effect – **DO NOT TITRATE DOSAGE FURTHER**
**third line agent only

Additional antihypertensive therapy

First line medicine	Recommended additional medicines
Bendrofluazide	Ramipril or Atenolol
Atenolol	Bendrofluazide or Amlodipine
Ramipril	Bendrofluazide or Amlodipine
Amlodipine	Ramipril or Atenolol

Cautions,conta-indications,side-effects and monitoring – see BNF 47

(ii)With macrovascular disease and/or diabetic nephropathy

Step (1) If not already on an ACEI/A2A initiate as follows:

(a)Check U and E's – if satisfactory start **RAMIPRIL** 1.25mg OD. Check U and E's after one week, if satisfactory increase the dose to 2.5-5mg OD.

(b)After a further 2-3 weeks recheck BP and U and E's – if satisfactory increase dose to 7.5mg OD if required. Check BP and U and E's after a further 1-2 weeks and increase dose to 10mg OD if required.

Recheck U and E's after a further 2-3 weeks.

A2A's – Patients who are intolerant of ACEI's should be commenced on **IRBESARTEN** 150mg OD and the dose increased to 300mg after one week.
U and E's should be checked before initiation of irbesartan and 1-2 weeks after.

NB: Do not start an ACEI/A2A if systolic BP<100mmHg, creatinine>200micromol/l, urea>12mmol/l, sodium<130mmol/l or potassium>5.0mmol/l. BP, serum creatinine and electrolytes should be checked within 2 weeks of a dose increase. If systolic BP is<100mmHg and the patient is symptomatic then decrease dose/discontinue therapy. If creatinine rises significantly(>40micromol/l or >20%) or potassium rises above 5.5mmol/l consider stopping ACEI or decreasing the dose.
If the patient complains of feeling dizzy on standing at any stage then check patient's erect and supine BP. If postural hypotension (difference of >10mmHg) then dose should be reduced or treatment discontinued.

Step (2) Add additional antihypertensive therapy as follows:

(a) Diuretic –
If serum creatinine normal start BENDROFLUAZIDE 2.5mg OD
" " > 125umol/l start FRUSEMIDE 20mg OD
(dose of frusemide may be increased to 40mg OD after 4 weeks if necessary)

(b)ATENOLOL 50mg OD

© **AMLODIPINE 5mg OD** increasing the dose after 4 weeks to AMLODIPINE 10mg OD if required for control of BP.

(d) DOXAZOSIN XL 4mg OD , increasing to DOXAZOSIN XL 8mg OD after one month if BP still above target. Dose may be further increased if necessary to 16mg OD.

(e) Ask patient to perform a 24hour urine collection to assess sodium excretion. If >200mmol/day counsel the patient regarding their dietary sodium intake.

2. ANTI-PLATELET THERAPY

Goal of therapy:
All patients should be on anti-platelet therapy once BP is relatively controlled (<160/90mmHg).

First choice:
Aspirin 75mg OD

Second choice:
Clopidogrel 75mg OD if patient has true aspirin allergy.

Counselling:
Take aspirin with or after food.

Cautions, contra-indications and side-effects:
See BNF 47

3. LIPID LOWERING THERAPY

Goal of therapy:
All patients greater than 40years old with type 1 or type 2 diabetes and/or coronary heart disease with a total cholesterol concentration > 3.5mmol/l should receive lipid lowering therapy to achieve the following target:

- **Reduction in total cholesterol of 25% and**
- **Total cholesterol level <5mmol/l**

Initial treatment:

SIMVASTATIN 40mg ON
Check LFT's before starting therapy and after 2-3months. Check plasma cholesterol also after 2-3 months. If the target has not been reached change to **ATORVASTATIN 10-40mg ON**. Recheck cholesterol levels and LFT's after a further 2-3 months. LFT's should be checked every 6-12 months thereafter.

Cautions,contra-indications and side-effects:
See BNF 47

Counselling:
Advice patients to report promptly unexplained muscle pain,tenderness and/or weakness.

b) Treatment protocol for the year 2005

DIABETES CARDIOVASCULAR RISK MANAGEMENT CLINIC
TREATMENT GUIDELINES

1.TREATMENT OF HYPERTENSION

Definitions:
Microalbuminuria: defined as a persistent rise (on 3 separate occasions) in urinary albumin loss to between 30 and 300mg/day.
To avoid a timed urine collection, a urinary albumin:creatinine ratio (ACR) > 2.5mg/mmol in men and 3.5mg/mmol in women is considered diagnostic provided there are no other causes eg. diabetic renal disease, urinary tract infection.

Diabetic nephropathy: defined by a persistently raised (on 3 separate occasions) urinary albumin excretion of > 300mg/day in a patient with or without a raised serum creatinine level and with co-existing diabetic retinopathy. An ACR > 30mg/mmol in a spot urine sample indicates diabetic nephropathy.

Goal of therapy:
To achieve the following BP targets:

Type 1 and 2 diabetes with no microalbuminuria –
target < 140/80mmHg
Type 1 diabetes with nephropathy – target < 120/70mmHg
Type2 diabetes with microalbuminuria – target < 135/75mmHg

(i)Without macrovascular disease

Initiation of treatment

STEP (1) : BENDROFLUMETHIAZIDE 2.5mg daily
Particularly effective in the elderly.
C/I's : Gout and moderate renal failure.

STEP (2) : Check U and E's, if satisfactory add LISINOPRIL 2.5mg OD.
Check U and E's after one week, if satisfactory increase the dose to 5 mg OD.
Increase to 10-20mg OD if required after a further 2 weeks after checking U and E's.
Particularly indicated for patients with heart failure and diabetic nephropathy.
C/I's : Renovascular disease, pregnancy,

A2A's – Patients who are intolerant of ACEI's should be commenced on CANDESARTAN 8mg OD and the dose increased to 16mg if required.
U and E's should be checked before initiation of CANDESARTAN and 1-2 weeks after.

NB: Do not start an ACE/Angiotensin-2 antagonist if systolic BP < 100mmHg, creatinine > 200 micromol/l, urea > 12mmol/l, sodium < 130 mmol/l or potassium > 5.0 mmol/l. BP, serum creatinine and electrolytes should be checked within 2 weeks of a dose increase. If systolic BP is < 100mmHg and the patient is symptomatic then decrease dose/discontinue therapy. If creatinine rises significantly
(> 40 micromol/l or > 20%) or the potassium rises above 5.5mmol/l consider stopping ACEI or decreasing the dose.
If the patient complains of feeling dizzy on standing at any stage then check patient's erect and supine BP. If postural hypotension (difference of > 10mmHg) then dose should be reduced or treatment discontinued.

STEP (3) : Add ATENOLOL 50mg OD.
Particularly useful for patients post-MI or with angina.
C/I's : Asthma, heart-block.

STEP (4) : Add NIFEDIPINE M/R 20-30mg OD increasing to maximum dose of 90mg OD if necessary at 2 monthly intervals.
Particularly useful in the elderly.
C/I : Unstable angina.

STEP (5) : Add DOXAZOSIN 1mg OD increased after 1-2 weeks to 2mg OD and thereafter to 4mg OD. A maximum of 16mg OD may be given if required.
Particularly useful for prostatism.
C/I's : Urinary incontinence.

Cautions, contra-indications, side-effects and monitoring – see BNF 48.

(ii) With macrovascular disease and/or diabetic nephropathy

STEP (1) : If not already on an ACEI/Angiotensin-2 antagonist initiate as detailed in section
" (i) Without macrovascular disease, " except that for diabetic nephropathy IRBESARTAN should be used instead of CANDESARTAN. IRBESARTAN should be initiated at 150mg OD and the dose increased according to response to 300mg OD after checking U and E's.

STEP (2) : If serum creatinine normal start BENDROFLUMETHIAZIDE 2.5mg OD.
If serum creatinine > 125umol/l start FUROSEMIDE 20mg OD (dose of FUROSEMIDE may be increased to 40mg OD after 4 weeks if necessary.)

STEP (3) : Add ATENOLOL 50mg OD.

STEP (4) : Add NIFEDIPINE M/R 20-30mg OD increasing to maximum dose of 90mg OD if necessary at 2 monthly intervals.

STEP (5) : Add DOXAZOSIN 1mg OD increasing after 1-2 weeks to 2mg OD and thereafter to 4mg OD. A maximum dose of 16mg OD may be given if required.

STEP (6) : Ask patient to perform a 24 hour urine collection to assess sodium excretion. If > 200mmol/day counsel the patient regarding their dietary sodium intake.

Positive indications and C/I's as for section "(i)Without macrovascular disease."

2. ANTIPLATELET THERAPY

(i) Without macrovascular disease

Goal of therapy :
Patients > 50 years with BP controlled to < 150/90 mmHg or patients with a 10 year risk of cardiovascular disease > 20% should receive antiplatelet therapy.

First choice :
Aspirin 75mg OD

Second choice :
Clopidogrel 75mg OD if patient has a true aspirin allergy.

Counselling :
Take aspirin with or after food.

Cautions, contra-indications and side-effects : see BNF 48.

(ii)With macrovascular disease and/or diabetic nephropathy

Goal of therapy :
All patients should be on anti-platelet therapy once BP is relatively controlled (< 160/90 mmHg).

Antiplatelet medication : as above.

3. LIPID LOWERING THERAPY

Goal of therapy :
All patients greater than 40 years old with type 1 or type 2 diabetes and/or coronary heart disease with a total cholesterol concentration > 3.5mmol/l should be considered for lipid lowering therapy to achieve the following target :

- Reduction in total cholesterol of 25% and
- Total cholesterol level < 5mmol/l

Initial treatment :

SIMVASTATIN 40mg OD
Check LFT's before starting therapy and after 2-3 months. Check plasma cholesterol also after 2-3 months. If the target has not been reached change to ATORVASTATIN 10-40mg ON. Recheck cholesterol levels and LFT's after a further 2-3 months. LFT's should be checked every 6-12 months thereafter.

Cautions, contra-indications and side-effects :
See BNF 48

Counselling :
Advise patients to report promptly unexplained muscle pain, tenderness and/or weakness.

Alison Cockburn,
Diabetes Cardiovascular Risk Clinic Pharmacist,WGH
January 2005

c) Treatment protocol for the year 2010

DIABETES CARDIOVASCULAR RISK MANAGEMENT CLINIC
TREATMENT GUIDELINES

1. TREATMENT OF HYPERTENSION

Definitions:
Microalbuminuria: defined as a persistent rise (on 3 separate occasions) in urinary albumin loss to between 30 and 300mg/day.
To avoid a timed urine collection, a urinary albumin: creatinine ratio (ACR) > 2.5mg/mmol in men and 3.5mg/mmol in women is considered diagnostic provided there are no other causes e.g. diabetic renal disease, urinary tract infection.

Diabetic nephropathy: defined by a persistently raised (on 3 separate occasions) urinary albumin excretion of > 300mg/day in a patient with or without a raised serum creatinine level and with co-existing diabetic retinopathy. An ACR > 30mg/mmol in a spot urine sample indicates diabetic nephropathy.

Goal of therapy:
To achieve the following BP targets:

Type 1 and 2 diabetes with no microalbuminuria –target < 140/80mmHg
Type 1 diabetes with nephropathy – target < 120/70mmHg
Type2 diabetes with microalbuminuria – target < 135/75mmHg

NB: type 1 or 2 diabetics with microalbuminuria with or without raised blood pressure require treatment with an ACEI or A2A.

Treatment of hypertension:

(i) Without macrovascular disease

Initiation of treatment:

STEP (1): BENDROFLUMETHIAZIDE 2.5mg daily
Particularly effective in the elderly.
C/I's: Gout and moderate renal failure.

STEP (2): Check U and E's, if satisfactory add LISINOPRIL 2.5mg OD
Check U and E's after one week, if satisfactory increase the dose to 5 mg OD.
Increase to 10-20mg OD if required after a further 2 weeks after checking U and E's.
Particularly indicated for patients with heart failure and diabetic nephropathy.
C/I's: Renovascular disease, pregnancy.

A2A's – Patients who are intolerant of ACEI's should be commenced on CANDESARTAN 8mg OD and the dose increased to 16mg if required.
U and E's should be checked before initiation of CANDESARTAN and 1-2 weeks after.

For diabetic nephropathy in type 2 diabetes, IRBESARTAN 150mg OD should be used increasing according to response to 300mg OD after checking U and E's.

NB: Do not start an ACE/A2A if systolic BP < 100mmHg, creatinine > 200 micromol/l, urea > 12mmol/l, sodium < 130 mmol/l or potassium > 5.0 mmol/l. BP, serum creatinine and electrolytes should be checked within 2 weeks of a dose increase. If systolic BP is < 100mmHg and the patient is symptomatic then decrease dose/discontinue therapy. If creatinine rises significantly (> 40 micromol/l or > 20%) or the potassium rises above 5.5mmol/l consider stopping ACEI or decreasing the dose.
If the patient complains of feeling dizzy on standing at any stage then check patient's erect and supine BP. If postural hypotension (difference of > 10mmHg) then dose should be reduced or treatment discontinued.

STEP (3): Add AMLODIPINE 5mg OD increasing to 10mg OD.
Particularly useful for elderly.
C/I's: Unstable angina.

STEP (4): Add DOXAZOSIN 1mg OD increased after 1-2 weeks to 2mg OD and thereafter to 4mg OD. A maximum of 16mg OD may be given if required.
Particularly useful for prostatism.
C/I's: Urinary incontinence.

STEP (5): Add SPIRONOLACTONE 25MG OD increasing to maximum dose of 100mg OD if necessary at 2 monthly intervals.
C/I's: Hyperkalaemia, hyponatraemia, Addison's disease.

STEP (6): Add ATENOLOL 50mg OD.
Particularly useful for patients post-MI or with angina.
CI: Asthma, heart-block.

Cautions, contra-indications, side-effects and monitoring – see BNF 48.

(ii) With macrovascular disease and/or diabetic nephropathy

STEP (1): If not already on an ACEI/A2A initiate as detailed in section "(i) Without macrovascular disease. "

STEP (2): If serum creatinine normal start BENDROFLUMETHIAZIDE 2.5mg OD.

If serum creatinine > 125umol/l start FUROSEMIDE 20mg OD (dose of FUROSEMIDE may be increased to 40mg OD after 4 weeks if necessary.)

STEP (3): Add AMLODIPINE 5mg OD increasing to 10mg OD if necessary at 4weeks.

STEP (4): Add DOXAZOSIN 1mg OD increasing after 1-2 weeks to 2mg OD and thereafter to 4mg OD. A maximum dose of 16mg OD may be given if required.

STEP (5): Add spironolactone 25mg OD. Increase to 100mg OD if necessary. Monitor U&E's in 7-14days after commencing or increasing dose.

STEP (6): Add ATENOLOL 50mg OD.

STEP (7): Ask patient to perform a 24 hour urine collection to assess sodium excretion. If > 200mmol/day counsel the patient regarding their dietary sodium intake.

Positive indications and C/I's as for section "(i) Without macrovascular disease."

2. ANTIPLATELET THERAPY

With macrovascular disease and/or diabetic nephropathy

Goal of therapy: All patients should be on anti-platelet therapy.

First choice: Aspirin 75mg OD
Second choice: Clopidogrel 75mg OD if patient has a true aspirin allergy.

Counselling: Take aspirin with or after food.
Cautions, contra-indications and side-effects: see BNF 48.

3. LIPID LOWERING THERAPY

Goal of therapy: All patients greater than 40 years old with type 1 or type 2 diabetes should receive lipid lowering therapy to achieve the following target:

- Reduction in total cholesterol of 25% and
- Total cholesterol level < 5mmol/l

Initial treatment: SIMVASTATIN 40mg OD.

Check LFT's before starting therapy and after 2-3 months. Check plasma cholesterol also after 2-3 months. If the target has not been reached change to ATORVASTATIN 10-40mg ON. Recheck cholesterol levels and LFT's after a further 2-3 months. LFT's should be checked every 6-12 months thereafter.

Cautions, contra-indications and side-effects: See BNF 57

Counselling: Advise patients to report promptly unexplained muscle pain, tenderness and/or weakness.

AC.22/06/10

Appendix 2: treatment protocols for the usual care

Cardiovascular Risk in Diabetes

Lipids

Hypercholesterolaemia is an important reversible risk factor for cardiovascular disease and should be tackled aggressively in all diabetic patients.

- In Type 1 patients, normal or high HDL-cholesterol concentrations are often seen. However an elevated HDL-cholesterol is not associated with the same cardio-protective effect as in non-diabetic individuals
- The characteristic hyperlipidaemia of Type 2 diabetes is mild hypercholesterolaemia, low HDL-cholesterol and hypertriglyceraemia
- Triglyceride concentrations are elevated by poor glycaemic control. Triglycerides may normalise with good glycaemic control, attention to diet and increasing exercise. Excess alcohol consumption is also associated with elevated triglyceride concentrations.

Screening for Dyslipidaemia

- Lipids should be checked at diagnosis and annually thereafter
- Assess more frequently if lipid-lowering therapy is prescribed
- Total cholesterol, HDL-cholesterol and triglycerides should be requested. For ease, non-fasting estimation is usually adequate. Lipids should not be screened in people whose life expectancy is estimated to be less than five years.

Management

1. Lifestyle Advice

- Reinforce **dietary advice** and optimise glycaemic control
- Provide weight reduction diet for those with BMI > 25
- If BMI > 30, set target of 5-10 kg weight loss
- Increase fruit and vegetable consumption (5 portions per day)
- Increase oily fish consumption (2 portions per week)
- Reduce saturated fat intake
- Encourage regular physical activity.

2. Exclude (and Treat) Secondary Causes of Hypercholesterolaemia

- Alcohol excess
- Hypothyroidism
- Nephrotic Syndrome
- Cholestasis
- Drugs (e.g. diuretics, corticosteroids)

3. Drug Treatment: Patients with existing cardiovascular disease (Secondary Prevention)

Includes diabetic patients with angina, myocardial infarction, cerebrovascular disease and peripheral vascular disease

- **Treat with a Statin if Total cholesterol >3.5 mmol/L**
- All patients with existing cardiovascular disease should take Aspirin. If aspirin is contraindicated, alternative antiplatelet therapy, such as clopidogrel, should be considered.

4. Drug Treatment: Patients without cardiovascular disease (Primary Prevention)

- Most people with Type 2 diabetes aged above 40 should receive treatment with a statin and it should be considered in people with Type 1 diabetes. A positive decision NOT to prescribe lipid-lowering therapy may be considered in people aged 40-50 years who have no other risk factors for CVD and in people with a particularly high HDL cholesterol (e.g. >1.8mmol/l)
- **Type 1 and Type 2 patients with evidence of nephropathy** (microalbuminuria or proteinuria present) are at particularly high cardiovascular risk and should be treated aggressively.

5. Age Limits

- There should be no 'upper age limit' for prescribing lipid-lowering therapy. Each individual should be considered on his/her own merits and, if life expectancy is estimated to be greater than five years, lipid-lowering therapy should be prescribed if standard criteria are met
- Once treatment is established, it should not be discontinued at any particular age, unless clinically indicated due to other conditions.

Patients with Persistently Raised Triglyceride Concentrations

- Check fasting sample (Total-cholesterol, HDL-cholesterol & Triglycerides)
- Optimise glycaemic control
- Exclude co-existing pathology e.g. alcohol excess.

Lipid Lowering Drugs

First line lipid-lowering therapy is Simvastatin Current NHS Lothian Lipid Management Guidelines state start with 40mg simvastatin at night. Atorvastatin should be commenced if patients fail to reach targets with Simvastatin. Monitoring of liver function and, if muscle pain, creatinine kinase is recommended.
Fibrates have been less well tested in clinical trials. They are mainly of benefit in those with mixed hyperlipidaemia and low HDL cholesterol. They may be considered in people who do not tolerate statin therapy.

Anti-platelet Therapy

Advice has been that Aspirin, or clopidogrel if aspirin intolerant, should be prescribed to patients whose 10 year risk of an event is >15%. However, the 2008 POPADAD trial shows that there is no benefit from daily prophylactic aspirin in type 1 or type 2 diabetes. This is borne out in advice from the drug and therapeutics bulletin.

Management of Hypertension for Type 1 or Type 2 Diabetes

Type 1 Diabetes

- In the absence of nephropathy (microalbuminuria or proteinuria), the prevalence of hypertension in Type 1 diabetes is similar to non-diabetic individuals
- Blood pressure rises as microalbuminuria becomes established
- Anti-hypertensive therapy reduces urinary albumin excretion and delays progressive loss of glomerular function. The greatest benefit is seen with ACE Inhibitors.

Type 2 Diabetes

- 40-50% of patients with Type 2 diabetes have hypertension at the time of diagnosis
- Hypertension accelerates the decline in renal function in established nephropathy.

Confirm the Diagnosis of Hypertension

Measurement of BP – see appendix 5 page 104

Thresholds and Targets for CV Risk in Diabetes

- The threshold for anti-hypertensive therapy is BP>140/90mmHg
- The target BP is <130/80mmHg in the absence of nephropathy
- In patients with Type 1 diabetes and nephropathy, ACE Inhibitors are first-line therapy and a target BP as low as possible is recommended

- In **uncomplicated patients** (no target organ damage, BP < 140/90mmHg), delay pharmacological intervention and reassess after 3-6 months of lifestyle measures
- If **target organ damage** (retinopathy, nephropathy, left ventricular hypertrophy) present, start anti-hypertensive therapy **immediately**
- If hypertension is **sustained or severe** (Diastolic BP > 110mmHg) or multiple cardiovascular factors are present, institute therapy **within 1-2 weeks**
- All hypertensive patients should receive lifestyle advice.

Diagnosis: Use of Ambulatory Blood Pressure Monitoring (ABPM)

- The average daytime BP and not the average 24 hour BP should be used to make treatment decisions
- BP measured by ABPM is systematically lower than surgery or clinic measurements in hypertensive patients; the average difference in techniques is 12/7mmHg; the target ABP is <130/80mmHg
- **Outcome trials in hypertension have all been based on surgery or clinic BP measurement, not on ABPM data.**

ABPM is available via the Edinburgh Direct Access ABPM service whereby GPs can refer patients to the Diabetes Out-patient Departments at the WGH, RIE and SJH. A recent study [1] involving patients attending the Direct Access service at the WGH found that results gained from Ambulatory Blood Pressure Monitoring were comparable with those for patients using self blood pressure monitors. Consequently self BP monitors are now routinely used instead of ABPM's as these are preferred by the majority of patients attending the Diabetes Out-patient clinics. The home BP monitors are used in accordance with the European Society of Hypertension guidelines whereby patients record their own BPs twice a day for seven consecutive days. The BPs recorded in the first two days are ignored and an average of the remaining BP's is calculated to give the average daytime BP measurement. Ambulatory Blood Pressure Monitors used are Spacelabs 90207 (Spacelabs Inc., Redmond, Washington, USA.) Self BP monitor used are Microlife Watch BP Home.

Ref.: McGowan,N and Padfield, PL. Self blood pressure monitoring: a worthy substitute for ambulatory blood pressure? J.Human Hypertension. Feb 2010

Treatment of Hypertension in Type 1 Diabetes

- All drugs effective, therefore choice should be tailored to individual patient's needs. For further information, see Lothian Joint Formulary.

If microalbuminuria or proteinuria is present in Type 1:

- ACE Inhibitors are first-line choice

- Angiotensin II antagonists can be used if ACE Inhibitors produce adverse effects e.g. cough
- Other classes of drugs may be added, with the exception of short acting dihydropyridine calcium channel blockers (e.g. Nifedipine), which are not as effective at limiting protein excretion.

Treatment of Hypertension Type 2 Diabetes

- All classes of drugs are effective at lowering BP, therefore choice should be tailored to individual patient's needs
- ACE inhibitors and long acting calcium channel blockers are the preferred first-line agents.
- ACE Inhibitors are the recommended first-line therapy if nephropathy is present, as they are reno-protective.
- Polypharmacy is likely: 30% will require 3 or more drugs to achieve target BP.

Management of Hypertension in the Elderly (Age 75+)

- Treating hypertension in the elderly confers protection against future stroke.
- Make a clinical decision on the relative benefits and risks of treating frail, very elderly patients
- Consider low dose Thiazide or long acting Calcium Channel Blocker as first line therapy
- Examine for signs of postural hypotension.
- BP targets may be relaxed.

Management of Isolated Systolic Hypertension

- Defined as SBP > 160 mmHg with DBP < 90 mmHg
- Common in middle-aged and elderly Type 2 patients
- Consider long acting Calcium Channel Blockers or low dose Thiazides diuretics for initial drug choice.

Indications for Hospital Referral

- Evidence of nephropathy (persistent microalbuminuria, overt proteinuria or serum creatinine > 150 µmol/L)
- Presence of cardiac failure or retinopathy
- Clinical possibility of renovascular disease or other secondary cause of hypertension
- BP difficult to control despite appropriate therapy
- Rise in serum creatinine (>50% from baseline) after ACE Inhibitor started

Use of ACE Inhibitors

- Consider the presence of renal artery stenosis in patients with Type 2 diabetes
- Suspect underlying renovascular disease if widespread atheroma present (e.g. carotid or abdominal bruits, aortic aneurysm, absent peripheral pulses)
- Before starting ACE Inhibitor, measure baseline urea, creatinine & electrolytes
- Repeat after 4-7 days, again after 3 months and thereafter annually
- Stop drug if significant hypotension or a significant rise in creatinine occurs (>50% from baseline)
- **Refer or discuss with secondary care physician if in doubt**

***SIGN recommend that ACE inhibitor therapy should be given to patients with diabetes who fall into any of the following categories:**

- following Myocardial Infarction (MI)

and should be considered in:

- heart failure due to left ventricular systolic dysfunction
- patients with stable angina

General Advice

- All classes of anti-hypertensive drugs are effective at lowering BP
- Select drug with once (or maximum twice) daily dosage to improve adherence.
- **Remember patients with diabetes are likely to be on multiple drugs**
- **Drug choices should, if possible, be tailored to an individual patient's needs e.g.**
  - ACE Inhibitor if previous MI with left ventricular dysfunction or persistent microalbuminuria or proteinuria present.
  - Cardio selective Beta-blocker or rate-lowering Calcium Channel Blocker if coexisting angina.
  - Thiazide diuretics are especially useful in older patients or patients with systolic hypertension. Bendroflumethiazide should not be prescribed in doses higher than 2.5mg daily.
  - Angiotensin II Receptor Antagonists should be reserved for patients experiencing adverse effects on ACE Inhibitors e.g. cough

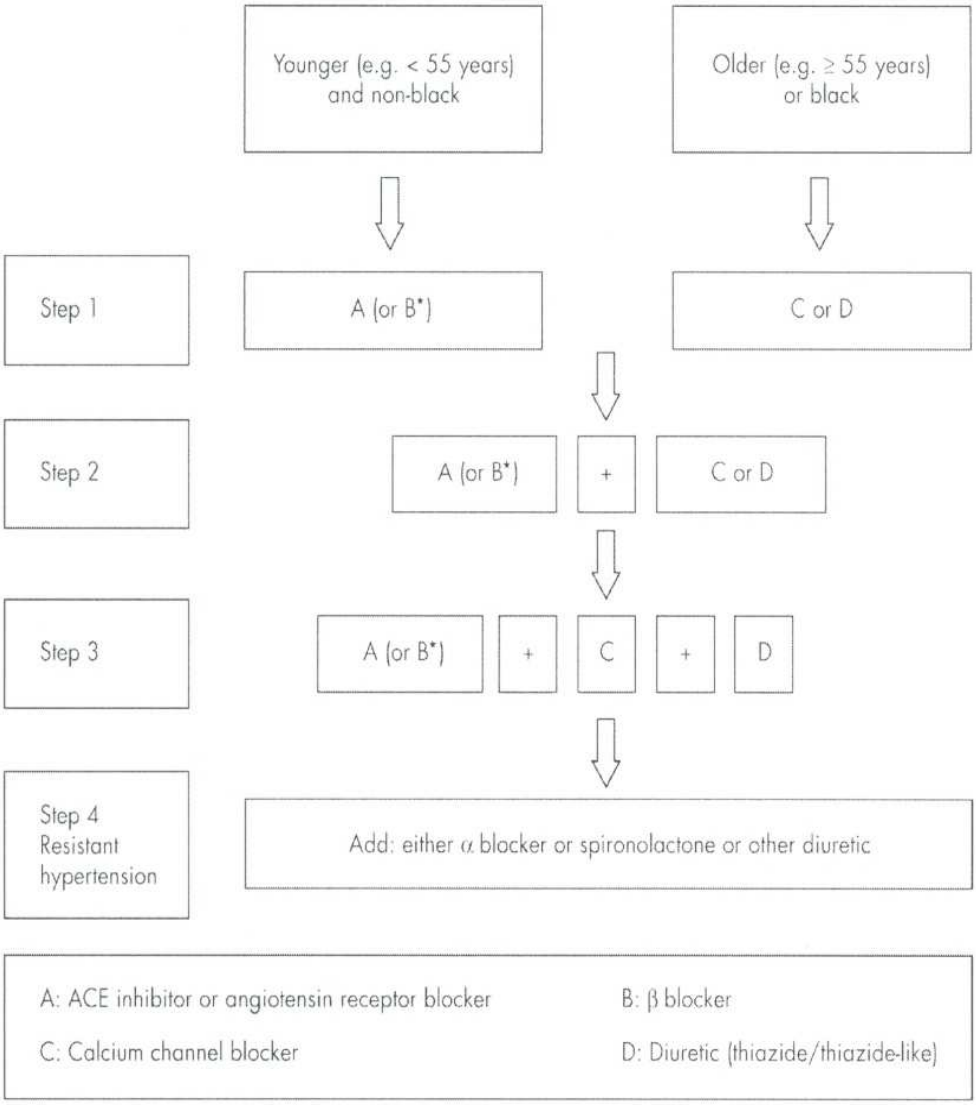
Dosage Adjustment

- An interval of at least 4 weeks should be allowed to observe the full response, unless it is necessary to lower BP more urgently
- The 2.5mg dose of Bendroflumethiazide should not be titrated up

Combination Therapy

- Less than half of patients with hypertension will be controlled by monotherapy
- Sub-maximal doses of two drugs result in larger BP responses and fewer adverse effects than maximal doses of a single drug
- Fixed dose combination preparations should be avoided due to cost and lack of flexibility in dose titration

Algorithm: Recommendations for combining blood pressure drugs/ABCD rule



*Combination therapy involving B and D induces more new onset diabetes compared to other combination therapies

*See **Appendix 5** (pg 104)for guidelines on measurement of blood pressure

Appendix 3: Ethical Approval

South East Scotland Research Ethics Service

Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG

NHS Lothian

Name: Moira Kinnear
Head of Pharmacy Education
Research & Development
Dept of Pharmacy
Western General Hospital
Edinburgh
EH4 2XU

Date: 31/08/2011
Your Ref:
Our Ref: NR/1108AB25a
Enquiries to: Alex Bailey
Direct Line: 0131 465 5679
Email: alex.bailey@nhslothian.scot.nhs.uk

Dear Moira,

Full title of project: Evaluation of a pharmacist-led cardiovascular risk clinic for patients with diabetes attending a hospital out-patient clinic

You have sought advice from the South East Scotland Research Ethics Service on the above project. This has been considered by the Scientific Officer and you are advised that, based on the submitted documentation (Evaluation of clinic draft 1.doc), it does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees in the UK. The advice is based on the following:

- *The project is an audit using only data obtained as part of usual care, but note the requirement for Caldicott Guardian approval for the use or transfer of person-identifiable information within or from an organisation*

If this project is being conducted within NHS Lothian you should inform the relevant local Quality Improvement Team(s).

This letter should not be interpreted as giving a form of ethical approval or any endorsement of the project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements. However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further. Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

You should retain a copy of this letter with your project file as evidence that you have sought advice from the South East Scotland Research Ethics Service.

Yours sincerely,

Alex Bailey
Scientific Officer
South East Scotland Research Ethics Service

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South East Scotland Research Ethics Service

DIFFERENTIATING AUDIT, SERVICE EVALUATION AND RESEARCH

November 2006

The "Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees" recommended NRES should develop guidelines to aid researchers and committees in deciding what is appropriate or inappropriate for submission to RECs, and NRES (with the Health Departments and with advice from REC members) has prepared the guidelines in the form of the attached table.

RESEARCH	CLINICAL AUDIT	SERVICE EVALUATION
The attempt to derive generalisable new knowledge including studies that aim to generate hypotheses as well as studies that aim to test them.	Designed and conducted to produce information to inform delivery of best care.	Designed and conducted solely to define or judge current care.
Quantitative research – designed to test a hypothesis. Qualitative research – identifies/explores themes following established methodology.	Designed to answer the question: "Does this service reach a predetermined standard?"	Designed to answer the question: "What standard does this service achieve?"
Addresses clearly defined questions, aims and objectives.	Measures against a standard.	Measures current service without reference to a standard.
Quantitative research -may involve evaluating or comparing interventions, particularly new ones. Qualitative research – usually involves studying how interventions and relationships are experienced.	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)
Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.
Quantitative research - study design may involve allocating patients to intervention groups. Qualitative research uses a clearly defined sampling framework underpinned by conceptual or theoretical justifications.	No allocation to intervention groups: the health care professional and patient have chosen intervention before clinical audit.	No allocation to intervention groups: the health care professional and patient have chosen intervention before service evaluation.
May involve randomisation	No randomisation	No randomisation
ALTHOUGH ANY OF THESE THREE MAY RAISE ETHICAL ISSUES, UNDER CURRENT GUIDANCE:-		
RESEARCH REQUIRES R.E.C. REVIEW	AUDIT DOES NOT REQUIRE R.E.C. REVIEW	SERVICE EVALUATION DOES NOT REQUIRE R.E.C. REVIEW

Appendix 4: project protocol

Project protocol

Evaluation of a pharmacist-led cardiovascular risk clinic for patients with diabetes attending a hospital outpatient clinic at the Western General Hospital, Edinburgh

Researcher

Ahmed Majid Alwan	Final year pharmacy student University of Tromsø, Norway

Supervisors

Alison Cockburn	Clinical supervisor and Lead Diabetes Cardiovascular Risk Pharmacist, NHS Lothian and Honorary Lecturer, University of Strathclyde
Moira Kinnear	Academic supervisor and Head of pharmacy Educations, Research & Development, NHS Lothian and Honorary Senior Lecturer University of Strathclyde
Alison Coll	Principal Pharmacist, Education, Research and Development, NHS Lothian

1. Introduction

Diabetes mellitus is chronic disease associated with severe morbidity and mortality. Diabetic patients are more likely to develop cardiovascular disease than non-diabetic patients[1].It is estimated that 4% of the NHS Lothian population have diabetes mellitus and the majority of these patients have type 2 diabetes mellitus [2]. The three main risk factors that increase the rate of development of cardiovascular disease are hyperglycaemia, dyslipidemia and hypertension. The pharmacist-led diabetes cardiovascular risk reduction (DCVR) clinics were established to control these risk factors and to reduce the incidents of cardiovascular disease.

The clinics co-operate with a multidisciplinary team to monitor patients, optimise treatments and prevent cardiovascular diseases, which makes the evaluation of the clinic's impact difficult.

Evaluations of the pharmacist led DCVR clinic have demonstrated a positive impact by optimising treatment, reducing blood pressure and improved lipid profiles [3 4].

This feasibility study intends to inform a future prospective randomised trial by assessing the feasibility of data collection from patient records of those who have attended the existing pharmacist-led DCVR clinic. The feasibility of outcome measures will be assessed (prescribing quality, pharmaceutical care issues, hospital admissions and consultations, changes in blood pressure and lipid measurements) to inform future power calculations.

2. Aim

2.1 To define outcome measures and the feasibility of data collection to inform a future randomised controlled prospective study to evaluate the pharmacist-led cardiovascular risk clinic.

2.2 To define the size of effect of the pharmacist-led DCVR on outcome measures such as proportion of patients reaching blood pressure target, proportion of quality standards reached for prescribing and hospital admission after discharge from the clinic to inform future power calculations.

2.3 To explore the feasibility of including economic evaluation.

3. Objectives

3.1 To characterise the diabetic population managed in NHS Lothian to include those who attend the secondary care diabetes clinics and those who attend or are eligible to attend to the pharmacist-led DCVR clinic

3.2 To compare outcome measures between patients eligible to attend the pharmacist-led DCVR clinic whom attend the secondary care diabetes clinic and patients who attend the pharmacist-led DCVR clinic in terms of admission rates after discharge from clinic, reasons for admission, length of hospitalisation, proportion meeting target blood pressure, time to achieve target blood pressure, lipid targets and drug related problems to inform future evaluation. To correlate with pharmaceutical care issues outcome measures between the two groups will be compared to explore the feasibility of future evaluation including economic evaluation.

3.3 To compare time to dialysis, changes in albuminurea and blood pressure in the subgroup of patients who attend the renal diabetic clinic between those who are referred to the pharmacist and those who are managed by usual care (secondary care diabetes clinic).

4. Subjects and Settings

The project is going to take place in the Western General Hospital, in the secondary care diabetes clinic and the pharmacist-led DCVR clinic.

The secondary care diabetes clinic operates on a daily basis Monday to Friday and can see up to 30 patients per half-day session. The patients are seen by doctors to initiate or to optimise diabetes treatment. The doctors can recommend changes to the cardiovascular medication as well as diabetes medications, these recommendation are sent to the GP to commence the changes at primary care. Patients can be viewed 2-3 times per year depending on their condition. If the patients are stable they will be offered only one review every year. A small number of patients are discharged every year to primary care.

Approximately 100 patients are referred to the pharmacist-led DCVR clinic per annum. The clinic operates once a week and can review 6 patients per clinic. The patients are seen by pharmacist who specialises in cardiovascular medications. An agreement with lead clinician for the diabetes clinic that the pharmacist will review and make recommendations to treatment related to diabetic cardiovascular risk. The changes recommended are sent to the GP to commence in primary care. Patients can be seen frequently, the clinic can offer a review every 6 weeks. Patients are discharged from the clinic after two consecutive visits where blood pressure is on target. Whilst attending the pharmacist led DCVR clinic patients continue their treatment at the diabetes clinic and at the GP clinic. Only few patients are referred back to the pharmacist led DCVR clinic. Patients are seen once of twice a year in the usual care.

The patients are going to be recruited retrospectively using the electronic patient record Scottish Care Information – Diabetes Collaboration (SCI-DC) database.

Inclusion criteria

The patients will be recruited retrospectively using the electronic patient record Scottish Care Information – Diabetes Collaboration (SCI-DC) database.

Patients managed by the clinic over a period of at least 12 months and discharged from the clinic for at least 3 years prior to the study commencing (discharged before January 2009).

Potential number of patients who might be eligible for future study will be estimated.

Advice will be sought from the scientific officer for the South East Scotland Research Ethics Service as to whether or not application for research ethics approval is necessary. If necessary an IRAS application will be made. If not, a clinical governance project proposal form will be completed and submitted through the Pharmacy Quality Improvement team (QIT) for approval.

Data will be anonymised in accordance with the data protection act. No patient identifiable details will leave the Western General Hospital (WGH).

5. Methods

5.1.1 Patients suitable for inclusion will be identified retrospectively from the SCI-DC database. A list of patients who have attended the pharmacist clinic from 2005 until 2009 will be generated from SCI-DC, any inappropriate candidates that do not match the inclusion criteria are going to be excluded.
Using SCI-DC a search will be performed to identify patients who have attended the Diabetes clinic in the year of 2007 and identifying the patients that would have been eligible to attend the pharmacist-led DCVR clinic and patients that do not fit the inclusion criteria are going to be excluded.

5.1.2 Data collection documents will be allocated an identification number linked to a list of patient names and date of birth to make it possible to collect additional patient information if required at a later period. The list of patient names will be kept in a locked filing cabinet within the Education, Research and Development department within the pharmacy department at the WGH. No patient identifiers are required for analysis. Anonymised data will be transferred onto a password accessed Microsoft Access database.

5.1.3 The general demographics of the population of patients who attend the secondary care clinic will be recorded and compared with those who attend or are eligible to attend the pharmacist's clinic. The demographics will include:

age, sex, type and duration of diabetes, co-morbidities, smoking habits, exercise habits and alcohol consumption.

5.2.1 From the evidence base the investigator will develop outcome measures.

5.2.2 Outcome measures will be agreed by the investigator and project supervisors.

5.2.3 The feasibility of data collection of outcome measures will be evaluated by accessing the SCI-DC database and using the pharmacist notes.

5.2.4 Outcome measures will be compared between patients attending the secondary care diabetes clinic and those attending the pharmacist-led DCVR clinic.

5.2.5 Outcome measures between the two groups will be compared and the feasibility of economic evaluation explored.

5.3.1 Patients who attended the secondary care renal diabetic clinic will be identified using Apex program.

5.3.2 Subgroup analysis between renal patients who attend the secondary care renal diabetes clinic and those attend the pharmacist-led DCVR clinic will be performed to compare time to dialysis, changes in albuminurea and blood pressure.

6. Analysis and findings

6.1 Descriptive statistical analysis will be used to describe the two groups including age, sex, smoking habits, alcohol consumption, duration of diabetes and co-morbidities.

6.2 The proportion of patients reaching blood pressure targets and other clinical parameters will be reported and compared between the two groups.

6.3 The proportion of patients reaching quality standards for prescribing will be reported and compared between the two groups.

6.4 The proportion of patients admitted to hospital following discharge from the clinic will be reported and compared between the two groups.

6.5 Sub-group analysis of the renal diabetic patients in terms of time to dialysis, change in albuminurea and change in blood pressure will be compared with patients attending the pharmacist-led DCVR clinic.

6.6 The feasibility of economic evaluation will be reported.

References

1) Scottish Intercollegiate Guideline Network (SIGN). Management of diabetes; March 2010
2) Lothian Diabetes Handbook 2010. A guide for Health Professionals managing diabetes in Lothian: august 2010
3) Mcgowan N, Cockburn A, Strachan M. WJ , Padfield P.L , Mcknight J.A. Initial and sustained cardiovascular risk reduction in a pharmacist-led diabetes cardiovascular risk clinic. The British Journal of Diabetes and Vascular Disease. 2008;8:34-38
4) Cockburn AJ, Mcknight JA, Kinnear M, LanniganNA, Strachan MWJ. Impact of a pharmacist-led cardiovascular risk reduction clinic on cardiovascular risk factor targets in people with diabetes. Diabetes UK Diabetic Medicine. 2005; 22 (2): 56–103

Appendix 5 detailed physiological results

Table 8 Physiological parameters

Parameter	Intervention group	Control group
Blood Pressure (mmHg)		
Number of patients	45	41
Mean SPB first appointment	155.09	150.85
	SD 19.02	SD 15.31
Mean SPB last appointment	135.91	142.51
	SD 10.39	SD 11.58
Mean DPB first appointment	80.38	88.32
	SD 10.31	SD 10.01
Mean DPB last appointment	71.02	81.54
	SD 7.79	SD 10.56
Number of patients reaching BP target	26	10
Kidney functions		
Mean Creatinine first appointment	116.70	72.61
	SD 52.01	SD 11.64
Mean Creatinine last appointment	123.56	79.23
	SD 56.05	SD 15.76
Mean change in Creatinine	6.85	6.61
	SD 19.38	SD 11.35
Number of patients	27	12
Mean ACR first appointment	22.5	11.62
	SD 47.80	SD 14.35
Mean ACR last appointment	19.61	6.15
	SD 50.54	SD 1.80
Mean change in ACR	2.89	5.47
	SD 29.27	SD 14.13
Number of patients	22	29
Lipids		
Mean cholesterol first appointment	4.57	4.88
	SD 0.95	SD 1.1
Mean cholesterol last appointment	4.43	4.44
	SD 0.86	SD 0.67
Mean change in cholesterol	0.14	0.69
	SD 0.76	SD 1.21
Number of patients	27	36
Mean HDL first appointment	1.22	1.14
	SD 0.27	SD 0.31
Mean HDL last appointment	1.15	1.83
	SD 0.22	SD 0.34

Continued table 8

Parameter	Intervention group	Control group
Mean change in HDL	0.073	0.44
	SD 0.11	SD 0.23
Number of patients	6	35
Mean Triglycerides first appointment	3.51	2.50
	SD 1.98	SD 1.08
Mean Triglycerides last appointment	3.19	1.92
	SD 2.09	SD 1.08
Mean change in Triglycerides	0.31	0.58
	SD 0.65	SD 1.38
Number of patients	7	36

Appendix 6 guideline non-adherence

The total number of antihypertensive guideline non-adherence in the intervention group was 86, deviation from the drug indicated by the guide line was the most prominent reason for none-adherence constituting 50% of the reasons for non-adherence. The type of antihypertensives prescribed to the patients before being referred to the pharmacist-led clinic corresponded to the same subclass of antihypertensive indicated in the pharmacist treatment protocol, but were not the same generic names as in the protocol. The number of the different reason for non-guideline adherence are summarised in table 9.

Table 9 Antihypertensive guideline non-adherence intervention group

Steps	**Drug**	**Choice**	**Unknown**	**Non-applicable**
Step 1	11	0	2	2
Step 2	7	4	3	4
Step 3	8	3	4	6
Step 4	16	0	0	5
Step 5	1	2	0	8

Table 10 Antihypertensive guideline non-adherence control group

Steps	**Drug**	**Choice**	**Unknown**	**Non-applicable**
Step 1	0	0	4	0
Step 2	0	0	7	1
Step 3	0	0	8	0
Step 4	0	0	5	0