MASTERPLAN: Multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners

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MASTERPLAN: Multifactoriële aanpak en doeltreffender behandeling van patiënten met nierschade met de hulp van gespecialiseerde verpleegkundigen
(met een samenvatting in het Nederlands)

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Contents

Preface

At the beginning of the twenty-first century it was recognized that cardiovascular morbidity and mortality are increased in patients with chronic kidney disease. This has stimulated several national and international organizations involved in the care for the CKD patient to issue guidelines with treatment advice. In this thesis the data are presented of a multicenter study that was initiated to investigate whether strict implementation of guidelines with the aid of a nurse practitioner supervised by a nephrologist could improve cardiovascular outcome. This study is known by the acronym MASTERPLAN: Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners.

The rationale of the study is given in Chapter 1.1, followed by a more detailed description of the study design in Chapter 1.2 and of the approach of the nurse practitioner toward lifestyle interventions in Chapter 1.3. The MASTERPLAN study was initiated under the assumption that many patients with CKD do not meet the treatment targets as advocated in the guidelines. This premise was shown in Chapter 1.3 and investigated more extensively in Chapters 2.1 and 2.2. Many patients did not attain treatment targets. Most notable, there were clear differences in the achievement of treatment goals between the nine centers. Possible explanations were explored and are discussed in chapters 2.1 and 2.2.

Lifestyle improvement and adherence to pharmacotherapy largely depend on actions of the patient. The driving force for these actions are derived from self-efficacy, the belief in ones own capabilities to actually successfully accomplish a certain task. In chapter 3 we investigated whether self efficacy in patients could be improved by an external intervention.

In chapter 4 the main results of the randomized study are discussed. In chapter 4.1 changes of cardiovascular risk factors during the initial two years of the study are

reported. In chapter 4.2 the results on major cardiovascular endpoints are presented and discussed.

Chapter 5 discusses the findings and provides perspectives for future studies, with emphasis on the role of nurse practitioner care.

Chapter 1.

Introduction

Chapter 1.1

Rationale and Design of the MASTERPLAN study

(Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners)

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J Nephrol. 2005 Jan-Feb;18(1):30-4.

Abstract

Background

Chronic kidney disease (CKD) is an established risk factor for cardiovascular disease. In addition patients with kidney disease are exposed to a myriad of risk factors that increase their risk even further. Treatment of risk factors in these patients is paramount to reducing cardiovascular risk and for attenuating progression of kidney failure. It is well known that lifestyle interventions are difficult, and that targets of medical treatment are seldomly met.
A multifactorial approach with the aid of nurse practitioners has shown to be beneficial for achievement of treatment goals and reduction of events in patients with diabetes mellitus and with heart failure. We propose that this will also hold for the CKD population.

Trial design

A multicenter randomized clinical trial will be performed to study whether intensive medical care delivered by a nurse practitioner and a nephrologist will reduce cardiovascular risk compared to care provided by the nephrologist alone. The acronym MASTERPLAN describes the study: Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners. Eight hundred patients will be randomized to physician care or nurse practitioner support.
For all patients the same set of guidelines and treatment goals apply. Both groups will receive treatment according to current guidelines and have access to specific cardioprotective medication. Nurse practitioners will intensify therapy by promoting lifestyle intervention, and meticulous implementation of relevant guidelines.

Patients will be followed for five years after baseline. Primary endpoints are all cause mortality, cardiovascular morbidity and cardiovascular mortality.

Introduction

Chronic kidney disease and cardiovascular disease

Chronic kidney disease (CKD) is a known risk factor for cardiovascular disease (CVD). This also applies for patients with mild kidney dysfunction. It has been established that already early in the process of kidney impairment damage to the cardiovascular system occurs. This suggests a gradual risk elevation with decreasing kidney function(1;2) Moreover, progressive development of atherosclerosis worsens CKD, thus constituting a vicious circle.

Multiple risk factors for CVD have been identified and are present in the CKD patient. They can be divided in traditional risk factors derived from the Framingham study (hypertension, dyslipidemia, diabetes, male gender, older age, smoking, obesity and positive family history for cardiovascular disease) and non-traditional risk factors, such as (micro)-albuminuria, anemia, homocysteïne, calcium and particularly phosphate imbalances, acute phase inflammation and oxidative stress.(1) In kidney transplant recipients (KTR) with kidney damage there is the additional effect of immunosuppressive drugs on CVD risk.(3) Given the very high risk of cardiovascular events in patients with CKD, active and multifactorial risk factor management is mandatory to reduce cardiovascular morbidity and mortality in this group.

Sub-optimal treatment

Most of the described risk factors can be modified. However, in daily practice the multitude of risk factors, the condition of the patient, the limited time available to

the physician and the amount of drugs necessary to modify CVD risk, hamper effective CVD-risk management in CKD patients. Several trials in hypertensive and dyslipidemic patients as well as in specified high-risk groups have shown that goals for treatment are often not met.(4;5) The same applies to CKD patients. In patients with kidney disease and established coronary disease only 45% of patients used aspirin, 25% used a HMG-CoA reductase inhibitor (statin) and only 64% used ACE inhibition or an angiotensin-receptor blocker (ARB).(6) In a pilot study among CKD patients of an outpatient clinic of a Dutch university hospital only 53% of patients with CVD were on aspirin, 66% used a statin and only 59% used ACE inhibition or an ARB. Only 45% of hypertensive CKD patients reached target blood pressures (unpublished data). In addition to drug treatment, lifestyle improvement has a beneficial effect on several risk factors like obesity, inactivity, smoking, hypertension, dyslipidemia and the development of glucose intolerance.(7) Implementation requires however intensive and prolonged coaching. Although not every patient will succeed in changing lifestyle, individual beneficial effects for those who succeed in improving lifestyle are evident.(7;8) Studies regarding lifestyle interventions in patients with CKD are lacking.

Multifactorial approach

It is clear that patients with CKD are exposed to multiple risk factors for cardiovascular disease and that physicians do not address these risk factors to their full extent. Although the contribution of one risk factor to cardiovascular risk in a certain patient may seem small, others have reported that the composite risk trough accumulation of several risk factors results in a very high risk for cardiovascular events.(1;9) Addressing multiple risk factors simultaneously indeed has a large impact on cardiovascular risk, as has recently been shown in patients with diabetes mellitus and in secondary prevention of CVD and heart failure.(10-

12) Strict regulation of hypertension, proteinuria or diabetes not only reduces cardiovascular risk but also attenuates the decline of kidney function.(13) A multifactorial intervention will undoubtedly result in improved preservation of kidney function and delay of renal replacement therapy. Although the importance of optimal implementation of treatment guidelines for CKD patients with high CVD risk has been stressed repeatedly, trials addressing this issue are lacking.(9;13) We outline the rationale and design of a randomized study dedicated to prevent cardiovascular events and reduce decline of kidney function in CKD patients.

Nurse practitioners

In daily practice physicians apparently do not have the time to address all relevant issues regarding the patient's disease and CVD risk profile in the time span of a regular outpatient visit. Therefore other ways to enhance CVD prevention should be investigated. The concept of case management by so-called nurse practitioners is a logical approach.

The benefits of coaching by nurse practitioners are evident in other high risk populations like patients with diabetes mellitus, patients with coronary artery disease and patients with heart-failure.(10-12;14;15) The extra time the nurse can invest in the patient and the emphasis on strict compliance to guidelines leads to improved adherence of patients to both lifestyle advice and risk modifying drugs.(11;12;14) This results in more patients reaching treatment goals, prevention or reduction of disease progression and reduction of cardiovascular events.(10;15)

The MASTERPLAN study

Trial objectives

The MASTERPLAN study is a multicenter randomized controlled trial to investigate a multifactorial approach that pursues maximal treatment through the implementation of guidelines with the aid of nurse practitioners. In MASTERPLAN, the effects of intensified treatment and coaching by nurse practitioners on cardiovascular morbidity, cardiovascular mortality and all-cause mortality in patients with CKD are studied. Secondary endpoints include changes in kidney function, changes in markers of vascular damage and changes in quality of life. A significant amount of kidney transplant recipients with a GFR within the inclusion criteria will be included in this trial.

Trial design

Eligible patients (CKD, estimated GFR by Cockcroft-Gault equation between 20 and 70 ml/min) will be randomized to nurse practitioner support or physician care. Eight hundred patients will be included and will be followed for five years. To all patients the same set of guidelines and treatment goals, represented in Table 1 and Table 2, apply. Both patients and physicians are provided with information about the beneficial effects of multifactorial risk factor management regardless of treatment allocation. In the intervention group nurse practitioners, supervised by a qualified nephrologist, will actively pursue lifestyle intervention (physical activity, nutritional counseling, weight reduction and smoking cessation), the use of specified cardioprotective medication and the implementation of current guidelines.

Table 1: Goals and relevant guidelines for cardiovascular risk factors in MASTERPLAN

Risk factors	**Goal**		**Guideline**
Blood pressure	</= 130/85 mm Hg[a]		NFN[b](16), KDOQI[c](17)
Proteinuria			KDOQI[c](17)
Protein excretion in urine	< 0.5 g/day		
Lipids			KDOQI[c](18;19)
Fasting LDL[d]	< 2.6 mmol/l		
Anemia			NFN[b](20), KDOQI[c](21)
Hemoglobin concentration	> 6.8 mmol/l AND </= 7.4 mmol/l[f]		
Glucose			NHG[g] (22)
Fasting glucose	< 7.0 mmol/l		
Non Fasting glucose	< 9.0 mmol/l		
Calcium/Phosphate metabolism			NFN[b](16), KDOQI[c](23)
Phosphate	</= 1.5 mmol/l		
PTH[e]	eGFR[h] > 30ml/min	< 7.7 pmol/l	
	15-30 ml/min	7.7-12.1 pmol/l	
	<15 ml/min	16.5-33 pmol/l	
Healthy Nutrition			NFN[b](24), GR[i](25)
Protein	0.8 –1.0 g /kg ideal bodyweight/ day		
Sodium excretion	100 mmol/24 hr		
Fat	Reduce fat, unsaturated fats preferred		
Energy	30-35 kcal/ kg ideal bodyweight/ day		
Overweight			
Body mass Index	<25 kg/m^2		
Physical activity	5x/week 30 minutes moderate activity		NNGB[j](26)
Smoking	To Quit		NFN[b](16)

A: In case of proteinuria > 1g/day: 125/75 mm Hg; B: NFN= Nederlandse Federatie voor Nefrologie (Dutch Federation for Nephrology); C: KDOQI= Kidney Disease Outcomes Quality Initiative; D: LDL = Low density lipoprotein; E: PTH = parathyroid hormone; F: In case of erythropoiesis stimulating agent use; G: NHG= Nederlands huisartsen genootschap (Dutch College of General Practitioners); H: eGFR= estimated Glomerular Filtration Rate; I: GR= Gezondheidsraad (Health Council of the Netherlands); J: NNGB = Nederlandse Norm voor Gezond Bewegen (Dutch Standard of Healthful Physical Activity)

They will check regularly if goals have been met and adjust treatment to achieve target values. Modification of therapy will be executed according to flowcharts that have been derived from current guidelines. Physician care comprises care conform the guidelines mentioned in Table 1 and Table 2.

The nurse practitioners are all qualified nurses with several years of experience and affinity for nephrology. They received extensive education in cardiovascular risk reduction with emphasis on current guidelines, they were familiarized with

the contents of the flowcharts and all were uniformly trained in interview techniques to aid them in implementing lifestyle-modification and maximizing compliance.

Table 2: Standard medication to reduce cardiovascular risk in MASTERPLAN

Medication	**Recommended dose**	**Point of impact**
Statin	e.g. atorvastatin 10 mg daily (or comparable dose of other statin)	Lipid-metabolism
Acetylsalicylic acid	80 mg daily	Thrombocyte aggregation
ACE inhibitor or Angiotensin Receptor Blocker	e.g. enalapril 5 mg twice daily (or comparable dose of other ACE inhibitor) or irbesartan 75-150 mg (or comparable dose of other ARB) daily	Blood pressure, renal function and cardiac pre- and afterload
Active vitamin D	e.g. alfacalcidol 0.25 μg daily if eGFR* is below 50 ml/min/1.73m^2	Bone-metabolism

*: eGFR= estimated Glomerular Filtration Rate

Patients with a kidney transplant within the last year, acute kidney damage or rapidly progressive glomerulonephritis and a malignancy less than five years ago other than a basocellular carcinoma of the skin are excluded.

Efficacy assessments

There are three primary efficacy endpoints in this trial: assessment of cardiovascular morbidity (comprised of myocardial infarction, stroke and all vascular interventions, including amputation of an extremity due to vascular insufficiency), cardiovascular mortality and all cause mortality. Secondary endpoints include: decline in kidney function, quality of life and markers of vascular damage. Decline in kidney function will be established by annual measurement of creatinine clearance by 24-hour urine measurements. Quality of life will be assessed using a validated questionnaire.(27) Markers of vascular

damage (aortic pulse wave velocity, carotid intima media thickness and the ankle-brachial index) will be measured annually.(28;29)

Sample size consideration

All analyses will be performed on an intention to treat basis. Interim analyses will be performed in the MASTERPLAN study based on time until the primary endpoint (with survival analysis).(30) The number of patients is estimated based on a power of 80%, a two-sided alpha of 0.05 and an absolute risk for cardiovascular events in the control arm of the study of 13.5% in five years.(31) To detect a reduction in this risk for cardiovascular events of 50%, which was also shown in a diabetic population, and taking into account a possible loss to follow-up of 15%, between 460 and 716 patients will have to be included.(10)

Conclusion

Cardiovascular risk in patients with CKD is extremely high, multifactorial in origin and present early in the course of CKD. Effectively addressing risk factors will reduce cardiovascular risk significantly. A multifactorial approach with the aid of nurse practitioners has been shown to be effective in other high-risk populations. The MASTERPLAN trial is designed to establish the effects of such a multifactorial approach in patients with moderate to severe kidney damage.

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Chapter 1.2

Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners [ISRCTN73187232].

Design of the MASTERPLAN STUDY

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Trials. 2006 Mar 30;7:8

Abstract

Background

Patients with chronic kidney disease (CKD) are at a greatly increased risk of developing cardiovascular disease. Recently developed guidelines address multiple risk factors and lifestyle interventions. However, in current practice few patients reach their targets.

A multifactorial approach with the aid of nurse practitioners was effective in achieving treatment goals and reducing vascular events in patients with diabetes mellitus and in patients with heart failure. We propose that this also holds for the CKD population.

Design

MASTERPLAN is a multicenter randomized controlled clinical trial designed to evaluate whether a multifactorial approach with the aid of nurse practitioners reduces cardiovascular risk in patients with CKD. Approximately 800 patients with a creatinine clearance (estimated by Cockcroft-Gault) between 20 to 70 ml/min, will be included. To all patients the same set of guidelines will be applied and specific cardioprotective medication will be prescribed. In the intervention group the nurse practitioner will provide lifestyle advice and actively address treatment goals. Follow-up will be five years. Primary endpoint is the composite of myocardial infarction, stroke and cardiovascular mortality. Secondary endpoints are cardiovascular morbidity, overall mortality, decline of kidney function, change in markers of vascular damage and change in quality of life. Enrollment has started in April 2004 and the study is on track with 700 patients included on October 15th, 2005. This article describes the design of the MASTERPLAN study.

Background

Patients with chronic kidney disease are at a greatly increased risk of developing cardiovascular disease (CVD).(1;2) This is most prominent in patients on kidney replacement therapy but also firmly established in patients with mild kidney dysfunction.(3) This increased cardiovascular risk in patients with chronic kidney disease (CKD) is the resultant of a multitude of risk factors. Among these risk factors are: all known traditional risk factors, a number of them evidently more prevalent than in the general population, risk factors that are associated with or worsened by kidney disease (anaemia, disturbances in calcium-phosphorus balance, oxidative stress, inflammation) and kidney disease itself.(4-7)
Several guidelines have been formulated, both nationally and internationally, to assist physicians in adequately reducing cardiovascular risk.(8-11) However it is well known that patients do not reach treatment-goals formulated in these guidelines.(12) This has also been established in patients with kidney disease.(13;14) In patients with diabetes mellitus and heart failure a multifactorial intervention implemented by nurse practitioners significantly improved metabolic control and reduced cardiovascular events.(15-18)
Given the high cardiovascular risk and the multitude of modifiable risk factors a multifactorial approach could very well also be of benefit for patients with CKD. This has been suggested several times but has never been proven.(4;19;20) Most risk factors that promote CVD also promote decline of kidney function. Effectively addressing these risk factors might therefore also delay kidney function decline.(21;22)

Design

The MASTERPLAN study is designed as a multicenter randomized controlled clinical trial with a duration of 5 years of follow-up.

Aims & primary outcome

The MASTERPLAN study aims to show that in patients with moderate to severe CKD strict implementation of current guidelines by a nurse practitioner, with emphasis on the use of cardioprotective medication and lifestyle changes, results in a reduction of a composite endpoint of myocardial infarction, stroke and cardiovascular mortality.

Cardiovascular morbidity, overall mortality, quality of life, percentage of patients achieving treatment goals, changes in kidney function and changes in markers of vascular damage will be considered as secondary outcomes.

Measurements

Changes in kidney function will be documented by annually measuring creatinine clearance from a 24-hour urine sample and measurement of the serum creatinine. Quality of life will be assessed through questionnaires that will be filled out by all participants annually. Markers of vascular damage will be recorded annually in a proportion of the patients. These markers address different aspects like endothelial function, arterial compliance and atherosclerosis in various vascular beds. Pulse wave analysis (PWA) and pulse wave velocity (PWV) will be measured in approximately 300 patients. Aortic pulse wave forms and aortic pulse wave velocity are indicators of arterial stiffness. PWV has been shown to be an independent predictor for cardiovascular risk.(23;24) PWA and PWV measurements have been validated and can be measured in a reproducible

manner.(25) Carotid intima media thickness (CIMT) evaluation through B-mode sonography will also be measured in approximately 150 patients. Increased CIMT is associated with an elevated risk of cardiovascular disease.(24) Change in CIMT has been shown to result from risk factor modifications in a variety of populations.(26) CIMT measurement has been validated and shown to be reproducible.(27)

Blood pressure will be recorded twice per year using a non-invasive automated oscillometric device. Patients will stay in a supine position for 30 minutes, blood pressure will be recorded every three minutes. The last five measurements will be used for analysis. Conventional office readings using the auscullatory method will also be documented.

Recruitment and Screening

All subjects will be recruited from the outpatient nephrology or internal medicine clinic of nine Dutch hospitals. Patients are identified by checking their medical records for compatibility with the inclusion criteria prior to a regular outpatient visit. Kidney function will be estimated using the Cockcroft-Gault formula (with a correction for body surface area as of April 15th 2005)(appendix B). The Cockcroft-Gault equation has been extensively validated and is generally appreciated as a useful tool to estimate creatinine clearance.(28;29) The physician will give every eligible patient a brief verbal explanation and extensive written information about the study. A week later follow-up by the nurse practitioner will be performed. Upon verbal consent to participate in the study, the patient will be invited to the office. In this visit the in- and exclusion criteria will be checked thoroughly, written informed consent will be acquired and subsequently baseline measurements will be performed. The medical ethics committees of the participating hospitals have approved the conduct of the study.

Recruitment began in April 2004 and is estimated to continue until December 2005. About 60% of patients deemed eligible by their physician and asked to participate in the study, actually participate and are included. The main reasons for non-participation appear to be: reluctance of the patient to changes in drug therapy and inability of the patient to attend the required visits. On October 15, 2005 700 patients had been included.

In- and exclusion criteria

Patients are eligible for inclusion when they fulfill the following criteria:

- The subject is at least 18 years old
- The subject is diagnosed with CKD with a creatinine clearance estimated by the Cockcroft-Gault equation between 20 and 70 ml/min.
- The subject is able and willing to provide written informed consent

The following conditions are considered exclusion criteria:

- A kidney transplantation less than a year before inclusion
- Acute kidney failure or rapidly progressive glomerulonephritis established by the treating physician
- Any malignancy less than five years before inclusion other than basocellular or squamous cell carcinoma of the skin.
- Participation in other clinical trials requiring the use of study medication

From April 15th 2005 until the end of the inclusion the Cockcroft-Gault equation was modified to take into account body surface area according to recent insights into the applicability of formulas to estimate kidney function.(30-33) This modification was approved by the medical ethics committee.

Table 1: Data collection

Visit	**Baseline 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Month	0	3	6	9	12
Informed Consent	x				
Demographic data	x				
Medical history	x				
In- and exclusion criteria	x				
Randomization	x				
Endpoints		x	x	x	x
Weight	x	x	x	x	x
Waist-hip ratio	x				x
Ankle-Brachial Index	x				x
RR and HR in sitting position	x	x	x	x	x
RR 30 minutes Dynamap	x		x		x
Smoking habit	x	x	x	x	x
Medication use	x	x	x	x	x
Three monthly Laboratory evaluation[a]	x	x	x	x	x
Annual Laboratory evaluation [b]	x				x
ECG	x				x
PWV (Proportion of patients)	x				x
Carotid-IMT (Proportion of patients)	x				x
Questionnaires [c]	x				x

a: Three monthly Laboratory evaluation: Hematology: Hb, Ht, trombocyte count; Chemistry: sodium, potassium, calcium, phosphate, bicarbonate, urea, creatinine, albumin; Urinalysis: spot urine creatinine, albumin, total protein

b: Annual Laboratory evaluation: Hba1c, uric acid, PTH, total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides; Urinalysis: 24 hr urine sodium, creatinine, albumin, total protein

c: Questionnaires: Quality of Life: SF-36, EQ-5D; Physical activity: SQUASH; Dietary composition; Erectile dysfunction

Baseline Evaluation and randomization

Table 1 summarizes the data collected at baseline evaluation. After the baseline evaluation, the patient will be randomized to either nurse practitioner care or physician care. Randomization to treatment is stratified by center and kidney transplant status using a web-based randomization module and performed in predefined blocks of certain numbers of patients.

Treatment groups

To all patients the same set of guidelines and treatment goals, represented in Table 2 and Table 3, apply.

Both patients and physicians were provided with information about the beneficial effects of multifactorial risk factor management regardless of treatment allocation. In the intervention group nurse practitioners, supervised by a qualified nephrologist, will actively pursue lifestyle intervention (physical activity, nutritional counseling, weight reduction and smoking cessation), the use of specified cardioprotective medication and the implementation of current guidelines. The nurse practitioner will check regularly whether treatment goals have been met and when deemed appropriate adjust treatment to achieve target values. Modification of therapy will be executed according to flowcharts that have been derived from current guidelines.

Physician care comprises 'usual care' conform the guidelines mentioned in Table 2. In contrast to the intervention group and in agreement with real life practice no extra incentives to adhere to the guidelines will be supplied.

Table 2: Goals and relevant guidelines for cardiovascular risk factors in MASTERPLAN

Risk factors	Goal		**Guideline**
Blood pressure	</= 130/85 mm Hg[a]		NFN[b](8), KDOQI[c](10)
Proteinuria			KDOQI[c](10)
Protein excretion in urine	< 0.5 g/day		
Lipids			KDOQI[c](11;34)
Fasting LDL[d]	< 2.6 mmol/l		
Anemia			NFN[b](35), KDOQI[c](36)
Hemoglobin concentration	> 6.8 mmol/l AND </= 7.4 mmol/l[f]		
Glucose			NHG[g] (37)
Fasting glucose	< 7.0 mmol/l		
Non Fasting glucose	< 9.0 mmol/l		
Calcium/Phosphate metabolism			NFN[b](8), KDOQI[c](38)
Phosphate	</= 1.5 mmol/l		
PTH[e]	eGFR[h] > 30ml/min	< 7.7 pmol/l	
	15-30 ml/min	7.7-12.1 pmol/l	
	<15 ml/min	16.5-33 pmol/l	
Healthy Nutrition			NFN[b](39), GR[i](40)
Protein	0.8 –1.0 g /kg ideal bodyweight/ day		
Sodium excretion	100 mmol/24 hr		
Fat	Reduce fat, unsaturated fats preferred		
Energy	30-35 kcal/ kg ideal bodyweight/ day		
Overweight			
Body mass Index	<25 kg/m^2		
Physical activity	5x/week 30 minutes moderate activity		NNGB[j](41)
Smoking	To Quit		NFN[b](8)

A: In case of proteinuria > 1g/day: 125/75 mm Hg; B: NFN= Nederlandse Federatie voor Nefrologie (Dutch Federation for Nephrology); C: KDOQI= Kidney Disease Outcomes Quality Initiative; D: LDL = Low density lipoprotein; E: PTH = parathyroid hormone; F: In case of erythropoiesis stimulating agent use; G: NHG= Nederlands huisartsen genootschap (Dutch College of General Practitioners); H: eGFR= estimated Glomerular Filtration Rate; I: GR= Gezondheidsraad (Health Council of the Netherlands); J: NNGB = Nederlandse Norm voor Gezond Bewegen (Dutch Standard of Healthful Physical Activity)

Table 3: Standard medication to reduce cardiovascular risk in MASTERPLAN

Medication	**Recommended dose**	**Point of impact**
Statin	e.g. atorvastatin 10 mg daily (or comparable dose of other statin)	Lipid-metabolism
Acetylsalicylic acid	80 mg daily	Thrombocyte aggregation
ACE inhibitor or Angiotensin Receptor Blocker	e.g. enalapril 5 mg twice daily (or comparable dose of other ACE inhibitor) or irbesartan 75-150 mg (or comparable dose of other ARB) daily	Blood pressure, renal function and cardiac pre- and afterload
Active vitamin D	e.g. alfacalcidol 0.25 μg daily if eGFR* is below 50 ml/min/1.73m^2	Bone-metabolism

*: eGFR= estimated Glomerular Filtration Rate

Clinical Data

The intervention group will receive follow up by the nurse practitioner as often as is indicated by the guidelines and the sort of lifestyle intervention the patient receives. Additional data will be collected for trial purposes quarterly as described in Table 1. The physician care group will receive an automated non-invasive blood pressure measurement two times a year. Annually each patient will be invited in the office to undergo a series of measurements and to fill out questionnaires. At the other time-points (represented in Table 1) present clinical data derived from the medical records will be recorded in the case report form.

The patients will fill out several questionnaires. Firstly quality of life will be assessed using the SF-36 (Dutch version) and EQ-5 D (Dutch version) questionnaires.(42;43) Secondly the Short Questionnaire to asses health enhancing physical activity will be given to subjects.(44) Thirdly a Food questionnaire developed by the Wageningen University will deliver information about the composition of the diet of the subjects.(45)

Data management

The entire study is performed according to the ICH-GCP guidelines, including on-site monitoring. The data will be documented in a case report form, via a validated web-based structure. Investigators will fill out the required data of a visit in an Internet application based on PDF files. Upon completing the form they will start the submission process. Before submission the data are verified and passed through an editing process to check for logical inconsistencies within the data. Any discrepancies need to be corrected before actual submission can take place. The data will be sent to a web server located in the data management center. The data are immediately transferred into a SQL server database.
The questionnaires are all in Teleform format and mailed to the data management center. Filled out questionnaires are scanned and data are immediately transferred to the same database used to store the clinical data. A specified validation procedure has been developed to check inconsistencies and to generate and process queries.

Endpoint collection and evaluation

The primary endpoint has been defined as follows, based on experience in other studies run at the UMCU.(46;47)

- Myocardial infarction is defined as evident new ischemic changes on an ECG or an established rise and fall pattern of cardiac enzymes.
- Stroke is defined as characteristic clinical symptoms of stroke accompanied by signs of recent ischemia using an appropriate imaging technique (CT-scan or MRI).
- Cardiovascular mortality is defined as death due to myocardial infarction, stroke, ruptured abdominal aneurysm, and terminal heart failure. Also sudden death will be regarded as part of cardiovascular mortality.

All suspected events, which might contribute to the primary endpoint, will be evaluated by an independent endpoint-committee (Appendix A). The committee will evaluate these events using definitions for the different events which are also used in other Dutch trials.(46;47)

Secondary endpoints are collected via clinical data, questionnaires or specified procedures. The SphygmoCor system (pulse wave velocity system and blood pressure analysis system, PWV Inc., Sydney Australia) is used to assess PWV and to analyze the arterial pulse contours. Pulse contours will be obtained by applanation tonometry at the carotid, radial and femoral arteries. Independent investigators blinded for treatment allocation of the subject will perform evaluation of recorded data. CIMT assessment will be performed using B-mode ultrasonography of both carotid arteries with a 7,5-MHz linear array transducer to assess the presence of plaques in the common carotid artery, bifurcation and internal carotid artery. All measurements will be recorded on video and evaluated off-line by independent evaluators blinded for treatment allocation of the patient.(48)

Nurse practitioners

The nurse practitioners are all qualified nurses with several years of experience and affinity for nephrology (Appendix A). They received extensive education in cardiovascular risk reduction with emphasis on current guidelines, they were familiarized with the contents of the flowcharts and all were uniformly trained in interview techniques to support them in implementing lifestyle-modification and maximizing compliance. Completion of the official Dutch Nurse Practitioner training program was no prerequisite to function as a nurse practitioner in this study.

Statistical and data analysis

Power analysis

To detect a 50% between-group difference in the trial primary endpoint with a pre-estimated 5-year event incidence of 13.5% for the control group (16;49), a power of 80% and a two-sided type I error α of 5%, at least 640 patients will have to be included. Taking into account a possible loss to follow-up of 15%, at least 740 patients will be randomized.

Group sequential analysis

Group sequential analysis will be used to evaluate the primary endpoints and to monitor the safety data. Sequential analysis is a statistical approach where one conducts significance tests over time as the data are collected. Sequential analysis and its application in clinical trials has been described extensively by Whitehead (50) . The general approach is as follows. A null hypothesis H_0 and an alternative hypothesis H_1 are formulated for a suitable measure θ of treatment difference. For this study with a survival type outcome variable, θ is equal to the logarithm of the hazard ratio (HR). H_0 is formulated as "no difference in the occurrence of the primary endpoints between the two trial arms" or $\theta = 0$ (i.e. HR = 1). The alternative hypothesis H_1 is formulated as $|\theta| \geq \log(0.48) = 0.73$ group. Two test statistics, Z and V, can be derived depending on the type of response variable. Z is a measure of the treatment difference; for survival data Z is the observed number of events in the control group minus the expected number of events given treatment equivalence (i.e. the number of events that would have occurred if the same proportion of events was found in the intervention group and in the control group).V reflects the amount of information about θ contained in Z; for survival data V is approximately equal to a quarter of the number of events observed. The

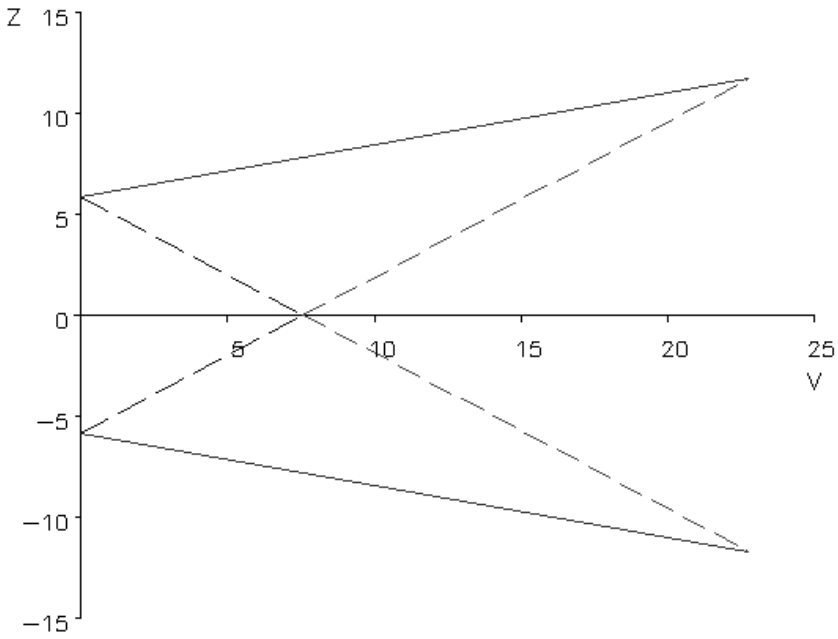
sequential analysis requires critical boundaries to be specified in advance. These boundaries depend on θ, the type I error α and the power 1-β. For each new group of patients, values of Z and V are calculated and presented graphically by plotting Z against V (see Figure1 for an illustration of a double-sided sequential test). Based on the path of cumulative (Z,V)-points, one of the following three decisions is made:

1) the upper or the lower (continuous) boundary is crossed: stop the data collection and reject the null hypothesis;
2) one of the inner wedge-shaped (dashed) boundaries is crossed: stop the data collection and accept the null hypothesis;
3) continue the data collection: the cumulative data are inadequate to draw a conclusion yet.

With a sequential approach a trial can be stopped earlier, on average, than with a fixed sample size approach. Using a sequential design between 460 and 716 patients would have to be included. The number of patients to be included cannot be fixed beforehand because patient data are analyzed cumulatively and a decision is made to stop or to continue the trial according to the interim results.
Due to the large difference between the duration of the inclusion period and that of the follow-up, it will not be possible to implement this potential benefit in the design of the trial. Although the length of follow-up in this trial in relation to the period scheduled for inclusion does not allow for a reduction in sample size other benefits of group sequential analysis remain present. Earlier clarity on the primary endpoint could allow for earlier stopping of the trial and thus result in saving time and funds for other experiments. Also safety related issues, which are to be monitored one-sided, will possibly be identified earlier and in this way patient safety is guaranteed throughout the trial.

Figure 1: illustration of a double-sided sequential test

Values of Z and V are calculated and presented graphically by plotting Z against V. Based on the path of cumulative (Z,V)-points one can decide to reject the null hypothesis (outer solid boundaries are crossed), accept the null hypothesis (inner dashed boundaries are crossed) or continue the study.



Statistical Methods

Group sequential (or interim) analyses will be performed using the double triangular test as described by Whitehead (50) and implemented in the computer program PEST version 4.(51) The analyses will be performed by an independent data safety monitoring board (DSMB) consisting of a nephrologist, an internist and a statistician (Appendix A). They meet every 6 months to monitor various aspects of the study, including recruitment, adverse events and interim analyses of the primary endpoints.

The results of the study will be analyzed following the 'intention to treat' principle. This means that subjects will be analyzed according to the group they have been allocated to by the randomization. Results will be presented as Kaplan-Meier curves for the two treatments and the difference between the treatments will be analyzed using a log-rank test. For the primary outcome variables the log-rank test will be adjusted for the effect of the cumulative data analyses. Results will be presented for all cause mortality and CV events separately.

The primary analysis of CIMT progression will be performed using a linear random coefficient (Laird-Ware) model using real visit days, treatment and clinical center as independent variables. For each participant, the intercept and slope of CIMT change over time is assumed to be a normally distributed random variable with different means for the two treatment groups. The mean slope for the nurse practitioner group will be compared to that for nephrologist-care group using linear contrasts and a 5% significance level. Additional exploratory analyses will evaluate the impact of including baseline IMT, lumen diameter, ultrasound reader, and center as additional co-variates.

The data analytic approach to arrive at the PWV outcome variable is similar to that of the CIMT outcome. Adjustments that will be taken into account in the estimates are changes in MAP and changes in heart rate, since both are closely related to PWV.

Discussion

Limitations of the study

There are several limitations to the study mostly due to unavoidable decisions.

1. Although many patients receiving standard care are not treated according to current guidelines it is ethically not possible to withhold information and advice on these guidelines from the control group. Therefore all

patients receive information about risk factor management and all physicians are informed about the treatment goals. This may result in improved treatment in the control group thereby attenuating the potential difference in cardiovascular events between the two treatment arms.

2. Due to the sort of intervention blinding is not possible for patients or physicians. This is unavoidable since some physicians will be treating or supervising both physician care and nurse practitioner care patients. Again, attenuation of group differences may occur.
3. The multifactorial intervention will make it impossible to single out one aspect of the intervention as being the most beneficial. Since trials establishing the exact amount of risk reduction per risk factor intervention are missing in patients with moderate to severe kidney dysfunction, such information would have been most useful. As pointed out earlier however the choice for a multifactorial design has received ample consideration. As a consequence of this choice for a multifactorial approach sample size is too small to allow for a definite statement about a single risk factor. A study large enough to establish the benefits of one aspect of the intervention would require thousands of patients and the logistics and funding necessary to realize this are not present for investigator driven research.

Conclusion

Cardiovascular risk in patients with CKD is very high, multifactorial in origin and present early in the course of CKD. Effectively addressing risk factors will reduce cardiovascular risk significantly. A multifactorial approach with the aid of nurse practitioners has been shown to be effective in other high-risk populations. The MASTERPLAN trial is designed to establish the effects of such a multifactorial

approach in patients with moderate to severe kidney damage. The MASTERPLAN trial is a unique multicenter randomized clinical trial because it investigates the effects of a multifactorial approach to reduce cardiovascular events in a population until now rarely targeted despite a huge cardiovascular risk. The employment of the nurse practitioner provides a valuable means of implementing the multifactorial intervention.

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Appendix A: Study organization

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- Dr. J.J. Beutler, nephrologist, Jeroen Bosch Hospital, 's Hertogenbosch (chair)
- Dr.J.D. Banga, internist, Hospital Gelderse Vallei, Ede
- Dr. A.P. Van Dijk, cardiologist, Radboud University Nijmegen Medical Center, Nijmegen
- Dr. J.W.M. Keunen, neurologist, Haga Hospital, Location Leyenburg, The Hague
- Drs. F.R. van Reekum, nephrologist, University Medical Center Utrecht, Utrecht

Data Safety and Monitoring Board

- dr. I. van der Tweel, department of biostatics, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands (chair)
- prof. dr. J.W. Lenders, department of internal medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
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Data management center

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Appendix B: Formulas to estimate creatinine-clearance

The Cockcroft-Gault equation

$$\text{Crcl(ml/min)} = \frac{(140 - \text{age (in years)}) \times \text{bodyweight (in kg)}}{72 \times \text{serum creatinine (in } \mu\text{mol/l)}} \times 88{,}5 \text{ (X 0.85 for females)}$$

The Cockcroft-Gault equation modified to correct for body surface area (effective from april 15th 2005).

$$\text{Crcl (ml/min/ 1.73 m}^2\text{)} = \frac{(140\text{-age}) \times \text{bodyweight (in kg)}}{72 \times \text{serum creatinine (in } \mu\text{mol/l)}} \times 88{,}5 \text{ (x 0.85 for females)} \times \frac{1{,}73}{\text{BSA}}$$

Body Surface Area will be estimated using the formula by Dubois and Dubois.

$$\text{BSA (m}^2\text{)} = 0.20247 \times \text{Height(m)}^{0.725} \times \text{Weight(kg)}^{0.425}$$

Chapter 1.3

MASTERPLAN: study on the role of nurse practitioners to implement a multifactorial intervention to reduce cardiovascular risk in chronic kidney disease patients.

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J Nephrol. 2008 May-Jun;21(3):261-7

Abstract

Moderate to severe chronic kidney disease (CKD) is associated with increased cardiovascular risk. Usually nephrologists are primarily responsible for the care of CKD patients. However in many cases treatment goals, as formulated in guidelines, are not met. The addition of a nurse practitioner might improve the quality of care. MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) is a randomized controlled multicenter trial, aimed at investigating whether a multifactorial approach in patients with moderate to severe CKD (stage 3 and 4) to achieve treatment goals using both a polydrug strategy and lifestyle treatment either with or without the addition of a nurse practitioner will reduce cardiovascular risk and slow decline of kidney function.

793 patients have been randomised to nurse-care or physician-care. In the nurse-care arm of the study, nurse practitioners use flowcharts to address risk factors requiring drug and/or lifestyle modification. They have been trained to coach patients by motivational interviewing with the aim to improve patient self management.

At baseline both treatment groups show equal distribution with regard to key variables in the study. Moreover in only 1 patient all risk factors were within the limits as defined in various guidelines, which underscores the relevance of our initiative.

Introduction

It is well established that patients with mild to moderate chronic kidney disease (CKD) have an increased cardiovascular risk.(1) A recent meta-analysis showed

that the absolute mortality risk increased exponentially with decreasing kidney function.(2) Apart from established risk factors, such as hypertension and dyslipidemia, there are also specific CKD related risk factors.(3;4) The recognition of these risk factors has resulted in treatment guidelines aimed to reduce both worsening of kidney function and risk of cardiovascular morbidity and mortality.(5-12) However, targets for the treatment of these risk factors have been derived from studies performed in populations other than CKD. Studies in CKD patients are lacking. Moreover, it is well recognized that in daily practice treatment goals formulated in guidelines are rarely met.(13;14) The need for randomized controlled trials to address the question whether cardiovascular risk can be influenced has been stressed several times.(15;16) In daily practice, the physician does not target a single risk factor but makes an effort to target all known risk factors. The real question facing the physician is thus not whether a single intervention is beneficial, but whether the whole package (i.e. all risk factors targeted according to the guidelines) results in an improvement of cardiovascular and/or kidney prognosis. In patients with diabetes mellitus such a multifactorial approach has been shown to result not only in an improvement of metabolic markers and blood pressure, but more importantly in a 50% (!) reduction of cardiovascular morbidity after 7.8 years of follow-up.(17) That such a reduction seems realistic is also supported by findings in a Canadian cohort study of elderly CKD patients.(18)

Care by nurse practitioners is increasingly implemented as a strategy to improve treatment, particularly in patients who have a clearly described treatment plan. They appear to perform as well as or even better than the physician.(19) Several explanations have been proposed. Firstly, they have more time for contact with and support of the patient. Secondly, the interaction between patient and care-

provider may be different in the case of a specialist nurse as compared to the physician, resulting in different behavior of the patient. Thirdly, nurses may have been specifically and therefore better trained in achieving lifestyle changes and/or adherence to treatment. Finally, they are more likely to follow guidelines precisely as compared to the physician. Physicians themselves can be a limiting factor in achieving treatment goals, at least with regard to blood pressure control. They may, for instance, be reluctant to change a medication regimen despite of inadequately controlled blood pressure, also known as therapeutic inertia.(20)

The aim of the current study is to investigate whether a multifactorial approach in patients with moderate to severe CKD (stage 3 and 4) to achieve treatment goals using both a polydrug strategy and lifestyle treatment with the aid of nurse practitioners will reduce cardiovascular risk and slow decline of kidney function. This is described in an acronym: MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners. Details of the study protocol are described elsewhere.(21;22) In the current paper, the approach of the nurse practitioners is discussed in more detail and baseline characteristics of the study participants are presented.

Subjects and Methods

Our study is a randomized controlled trial performed in nine Dutch hospitals. The results of the treatment regimen executed by a specialized nurse under supervision of and in collaboration with a nephrologist is compared with the care delivered by the patient's own physician, which is mostly a nephrologist. In both arms of the study the same sets of guidelines apply. The primary endpoint is a composite of fatal and non-fatal myocardial infarction, stroke and cardiovascular mortality.

Secondary endpoints are all cause mortality, achievement of treatment goals for the various risk factors, decline of kidney function and quality of life. The trial is registered with www.controlled-trials.com [ISRCTN73187232]. Ethics committee approval was obtained as well as written informed consent of all participants. Reported endpoints are adjudicated by an independent committee. Endpoints will be analyzed by group sequential (or interim) analyses using a double triangular test.(23;24) The results of the study will be analyzed following the 'intention to treat' principle, i.e. that subjects will be analyzed according to the group they have been allocated to by the randomization.

Sample size estimate is based upon the assumption of an absolute event rate of 13.5 % in 5 years for the primary endpoint in the control-group.(25) An estimated reduction of incidence of the primary endpoint of 50% in the intervention-group, an alpha of 0.05 and a beta of 80%. The power calculation based upon conventional cox-proportional hazard analysis showed that approximately 682 patients were needed with an estimated follow-up of 5 years. Taking into account 15% loss to follow-up because of non-endpoint death or other reasons, approximately 800 patients were required. In earlier publications other sample sizes based upon the application of sequential analysis were described.(22)

Patients were eligible for inclusion if they had a diagnosis of CKD with an estimated creatinine clearance between 20 and 70 ml/min/1.73m^2 using the Cockgroft-Gault equation adjusted for body surface area.(26;26) Patients were excluded if they had kidney transplantation in the year prior to randomization or had a malignancy other than basocellular or squamous cell carcinoma of the skin in the five years prior to randomization. All patients were recruited from outpatient departments of nephrology or internal medicine.

Table 1: Goals and relevant guidelines for cardiovascular risk factors in MASTERPLAN

Risk factors	**Goal**	**Guideline**
Blood pressure	</= 130/85 mm Hg[a]	NFN[b](12), KDOQI[c](27)
Proteinuria		KDOQI[c](27)
Protein excretion in urine	< 0.5 g/day	
Lipids		KDOQI[c](5;28)
Fasting LDL[d]	< 2.6 mmol/l	
Anemia		NFN[b](29), KDOQI[c](30)
Hemoglobin concentration	> 6.8 mmol/l AND </= 7.4 mmol/l[f]	
Glucose		NHG[g] (31)
Fasting glucose	< 7.0 mmol/l	
Non Fasting glucose	< 9.0 mmol/l	
Calcium/Phosphate metabolism		NFN[b](12), KDOQI[c](32)
Phosphate	</= 1.5 mmol/l	
PTH[e]	eGFR[h] > 30ml/min < 7.7 pmol/l	
	15-30 ml/min 7.7-12.1 pmol/l	
	<15 ml/min 16.5-33 pmol/l	
Healthy Nutrition		NFN[b](33), GR[i](34)
Protein	0.8 –1.0 g /kg ideal bodyweight/ day	
Sodium excretion	100 mmol/24 hr	
Fat	Reduce fat, unsaturated fats preferred	
Energy	30-35 kcal/ kg ideal bodyweight/ day	
Overweight		
Body mass Index	<25 kg/m^2	
Physical activity	5x/week 30 minutes moderate activity	NNGB[j](35)
Smoking	To Quit	NFN[b](12)

A: In case of proteinuria > 1g/day: 125/75 mm Hg; B: NFN= Nederlandse Federatie voor Nefrologie (Dutch Federation for Nephrology); C: KDOQI= Kidney Disease Outcomes Quality Initiative; D: LDL = Low density lipoprotein; E: PTH = parathyroid hormone; F: In case of erythropoiesis stimulating agent use; G: NHG= Nederlands huisartsen genootschap (Dutch College of General Practitioners); H: eGFR= estimated Glomerular Filtration Rate; I: GR= Gezondheidsraad (Health Council of the Netherlands); J: NNGB = Nederlandse Norm voor Gezond Bewegen (Dutch Standard of Healthful Physical Activity)

All physicians of the participating patients received the treatment guidelines with specific targets as indicated in Table 1.

In these guidelines the targets are specified. Of note, the guidelines include mandatory use of acetylsalicylic acid, ace-inhibition and a statin. In every participating center a specialized nurse has been appointed. She/he is responsible for the treatment regimen which is aimed to achieve the specified goals.

The patients who have been assigned to nurse care are monitored at least every three months, and more often if the nurse considers this necessary. The physician care group is only seen once yearly by a study nurse and the physician decides upon the frequency of visits. The nurse will meet the patient in the control-group solely for the purpose of performing study-measurements (blood pressure, ankle brachial index, pulse wave velocity) thus assuring a standardized measurement within one center of certain risk factors. No further comments with regard to adherence of guidelines will be provided by the nurses in the control group.

Nurse practitioners

The aims of the contacts of the nurse practitioners with the patients are to pursue strict adherence to guidelines and to modify lifestyle if necessary.
In prior studies a lifestyle intervention was only moderately successful at best.(17) Most of these programs (including the Steno-2 study) however applied a strict format for lifestyle-change with a fixed number of sessions at fixed intervals.(36) Moreover often simultaneous interventions were performed like improving diet, stimulate physical exercise and quit smoking. The process of lifestyle change in our study is based upon two pillars. The central issue is self management of the patient.(37) The patient is approached as an equal partner in the treatment plan. They can choose if and how they want to modify their lifestyle. The role of the care-provider is to assist the patient by improving motivation. Motivational interviewing is the technique to enhance motivation to make a change and to increase the chance of success. There are 5 key characteristics in the technique:(38)

- express empathy: to acknowledge that each client has her/his unique perspective, feelings, and values.

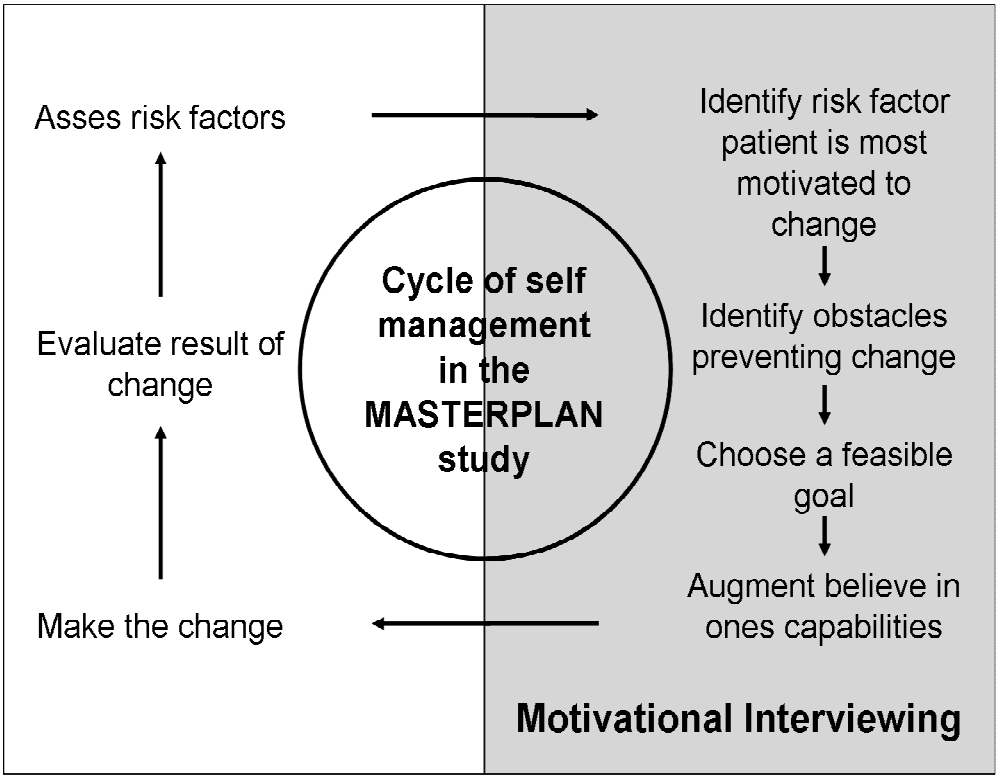
- develop discrepancy: to help the client focus her/his attention on how current behaviour differs from ideal or desired behaviour.
- avoid argumentation: to accompany the client through the process of change, not to "drag" him/her along.
- roll with resistance: to avoid the generation of resistance as much as possible, and divert the energy that the client is investing in resistance, towards positive change.
- support self-efficacy: to elicit and support hope and optimism in the feasibility of accomplishing change. This requires the nurse to recognize the client's behavioral strengths and bring these to the forefront as much as possible.

The second pillar is the cycle of change (Figure 1). Improving lifestyle can be difficult and thus only one aspect will be targeted at a time. The patient is encouraged to improve his lifestyle in concordance with his motivation and possibilities, even if this only results in a modest change (i.e. reducing weight with only 2 kg in an obese patient). In a following cycle the positive emotion, which resulted from the previous successful changes is used to achieve another (and possibly more substantial) improvement. No prospective trials applying motivational interviewing in a multifactorial approach particularly in CKD patients have been reported yet.

All study nurses are experienced in nephrology or vascular medicine. Completion of the official Dutch training program for nurse practitioners was not a prerequisite for participation as a nurse in MASTERPLAN. They received extensive education in how to improve self management, to perform motivational interviewing and to improve cardiovascular risk management. They were familiarized with the contents of flowcharts, which describe targets, suggest drugs and dosages and also indicate frequency of consultation and laboratory evaluations.

Figure 1: Cycle of change in the MASTERPLAN-study.

After assessment of risk factors together with the nurse practitioner, the patient chooses which risk factor to what extent will be targeted. After a (successful) attempt to change a new assessment will be made and the cycle starts again. The grey area describes where motivational interviewing as a tool is applied by the nurse practitioner to achieve optimal results.



However, in concordance with Dutch legislation, nurses are not allowed to prescribe medication. Every contact requiring a change in medication or every medical situation not covered by the flowcharts needs to be approved by a nephrologist.

Twice yearly the nurses are further trained and updated in cardiovascular risk management, in aspects of patients self management and in motivational interviewing. The latter is done by an experienced coach.

Results

Patient inclusion was between April 2004 and December 2005, in this period 793 participants were randomized. Inclusion per center ranged from 65 to 105 patients. Five patients were excluded shortly after randomization because they withdrew consent or did not meet the inclusion criteria. Thus 788 patients are available for follow up. During the conduct of the study, loss to follow up is less than expected. On January 1st 2008 only 11 were lost because of various reasons, mostly withdrawal of consent.

At baseline 91% of patients had CKD stage 3 or 4 (n=477 and 240 respectively), 7% had CKD stage 1 or 2 and 2% had stage 5. Baseline characteristics are represented in Table 2. It can be concluded that the randomization procedure was effective in creating two comparative populations with regard to the treatment goals evaluated in this study. The observed difference of prevalence of cardiovascular disease history is present because of chance despite the randomization process.

34 % of non-proteinuric patients achieved the BP-goal, whereas the same applies for 14% of proteinuric patients (37% of the cohort has proteinuria). The phosphate and hemoglobin goals are attained in the large majority of patients (90% en 92% respectively). Approximately 50% of patients reached the LDL-cholesterol goal and the PTH goal.

With regard of lifestyle modifiable risk factors, 21% of patients used tobacco regularly, 67% had a BMI over 25 kg/m^2 and 22 % even had a BMI over 30, 83% of patients had a urinary sodium excretion over 100 mmol/day.

We evaluated achievement of 11 treatment goals at baseline: blood pressure proteinuria, LDL-cholesterol, glycemic control, hemoglobin, serum phosphate, serum PTH, sodium excretion, BMI, adherence to guidelines of healthy physical activity and not smoking.

Table 2. Characteristics of Participants at Baseline by assigned treatment.

Parameter	**Control group (n=393)**	**Intervention group (n=395)**
Age (yrs)	59.3 (12.8)	58.9 (13.1)
Gender (male) (%)	68	67
Race (Caucasian)	93	91
Nephrological diagnosis (%)		
Diabetic nephropathy	9	11
Renovascular	28	26
Glomerulonephritis/ interstitial nephritis	34	28
Congenital disease	13	11
Unknown	16	24
Kidney transplantation (%)	14	14
Prior cardiovascular disease by questionnaire (%)	25	33
Creatinine (mcmol/l)	181 (67)	182 (64)
eGFR (ml/min/1.73m^2)[a]	37.7 (14.0)	38.4 (15.2)
Office BP (mm Hg)	139 (22)/ 81 (11)	138 (20)/ 80 (11)
Oscillometric BP (mm Hg)	136 (21)/ 79 (11)	135 (20) / 78 (11)
Proteinuria (g/24 hr)[c]	0.3 [0.1-0.8]	0.2 [0.1-0.8]
LDL-cholesterol (mmol/l)	2.74 (0.90)	2.78 (0.95)
Haemoglobin (mmol/l)	8.2 (1.0)	8.2 (1.0)
History of DM (%)[b]	23	26
Phosphate (mmol/l)	1.10 (0.24)	1.10 (0.25)
PTH (pmol/l) [c]	9 [5-14]	9 [5-15]
Sodium-excretion (mmol/24 hr) [c]	150 [113-189]	148 [116-195]
BMI (kg/m^2)	27.2 (4.9)	27.0 (4.6)
Physical activity (%) [d]	60	57
Smoking (%)	24	19

Values are proportions, means with corresponding standard deviation, or median with inter quartile ranges, when appropriate.
Abbreviations: eGFR= estimated glomerular filtration rate, BP = blood pressure, DM= diabetes mellitus, PTH = parathyroid hormone, BMI = body mass index
[a] Based on the MDRD formula
[b] History of diabetes mellitus defined as using blood glucose lowering medication or fasting glucose >7.0 mmol/l.
[c] median [25th -75th percentile]
[d] adherence to Dutch physical activity guideline

At baseline, only 1 patient reached all 11 treatment targets. Approximately two-third of the patients did not achieve 4 or more treatment-goals.

Discussion

It has been recognized that treatment goals for various diseases are often not met. This has also been shown in CKD patients, both in a Canadian population and more recently in a southern European population.(13;14) The analysis of the baseline data of our study indicates that the same holds for Dutch patients. Considerable proportions of patients do not achieve the various medication and lifestyle modifiable goals. This frequently occurring undertreatment combined with the expected increase of patients with CKD stage 3-4, demands a new approach towards the care of the CKD patient. One possible solution is the addition of specialized nurses to the team with the task to implement a multifactorial risk reduction program and to achieve goals formulated in guidelines. In the MASTERPLAN study, we implement nurse practitioner care in a prospective randomized fashion, and hope to show that this not only results in more complete adherence to guidelines but also that it results in an improvement of cardiovascular and kidney prognosis.

The use of nurses to coach the patient may be beneficial for several reasons as outlined earlier. The design of the MASTERPLAN study however does not permit to identify the one or more targeted risk factor(s) that are responsible for the clinical effects (if any).

There are some other limitations to MASTERPLAN. Since it is ethically not acceptable to withhold information from the patient about risk factors and treatment goals, all patients received information on risk factor management and all physicians are informed on the treatment goals. This may result in an improvement in treatment in the control group. Moreover, due to the type of intervention, blinding is not possible for both patients and physicians. Both effects

could attenuate the potential difference in outcome between the two treatment arms.

Conclusion

The MASTERPLAN study aims at investigating whether a multifactorial risk intervention with the aid of nurse practitioners can reduce the incidence of cardiovascular events and slow worsening of kidney function in CKD patients. At baseline in only 1 of patients all 11 risk factors were within the limits as defined in various guidelines, this underscores the relevance of our initiative.

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Chapter 2.

Baseline data

Chapter 2.1

Quality of care in patients with chronic kidney disease is determined by hospital specific factors

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Abstract

Background

Guidelines have set goals for risk factor management in chronic kidney disease (CKD) patients. These goals are often not met. In this analysis we set out to assess the quality of risk factor management in CKD and to identify factors that determine the quality of care (QoC). For that purpose, baseline data of the MASTERPLAN study have been used. MASTERPLAN is a multicenter study which evaluates the effect of a multifactorial intervention in prevalent CKD patients on cardiovascular (CV) events and progression of kidney failure.

Methods

QoC was quantified using a score based on the number of 11 defined treatment goals on target. The maximum score per patient was 11.

Results

The average (± SD) QoC score was 6.7 (±1.5). The average score per center ranged from 5.9 to 6.9. In a multivariable analysis center proved to be a significant, independent determinant of QoC with a difference up to 0.7 between centers. This difference remained when adjustments were made for those risk factors primarily treated by pharmacotherapy. Other factors that were significantly related to the quality of care were eGFR, Caucasian race, diabetes mellitus, diabetic nephropathy as cause of kidney disease, and previous kidney transplantation.

Conclusions

In CKD patients, risk factors for progression of kidney failure and CV events were inadequately controlled. Treatment center proved to be an important determinant

of QoC. This data may point towards the physician's interest and preference as important determinants of QoC. This is a potentially modifiable determinant of the quality of patient care. [Trial registration ISRCTN registry: 73187232 (http://isrctn.org)]

Introduction

Management of chronic diseases such as diabetes, hypertension and chronic kidney disease (CKD) is difficult. For all these disease conditions, treatment guidelines are defined, but treatment goals are often not achieved. Identifying factors predictive for the quality of the prescribed and the achieved care may help to improve the overall quality of care (QoC). We had the opportunity to study this in some detail in a group of CKD patients.

The guidelines for treatment of CKD patients aim to reduce the risk of progression of kidney failure and of cardiovascular (CV) morbidity and mortality.(1-6) The risk factor profile includes factors targetable by pharmacological intervention and by lifestyle changes. However, in patients with CKD, as well as in other patient groups, treatment goals are often not met.(7-9) Various factors have been suggested as contributing factors, including: patient characteristics (gender, age and comorbidity), hospital characteristics (teaching versus non teaching, profit versus non-profit); regional or country specific aspects and physician's preferences and interest.(9-11) Since detailed information on these issues is not available, we set out to study the quality of risk factor management in patients with CKD and to identify factors that may determine QoC. In that respect, we were particularly interested in risk factors accessible for improvement. We used the baseline data of the MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) study, a randomized,

controlled multicenter study evaluating the added value of nurse practitioner care in reducing CV events and attenuating the decline of kidney function in patients with prevalent CKD.

Subjects and Methods

MASTERPLAN study

The MASTERPLAN study is a randomized controlled trial conducted in nine centers with a nephrology department in the Netherlands. Rationale and design have been published elsewhere.(12;13) Ethics committee approval was obtained as well as written informed consent of all participants.

In brief, adult patients with moderate or severe CKD (estimated GFR (eGFR) by Cockcroft-Gault equation between 20-70 ml/min) seen in an outpatient clinic by a nephrologist or general internist were included. All participating hospitals were teaching hospitals that offered a full range of nephrology treatment including kidney replacement therapy (both hemodialysis and peritoneal dialysis) and were involved in the care of kidney transplant recipients. Three centers were university clinics that offered tertiary care and had kidney transplant programs. The number of beds per hospital ranges from 414 to 953. The 6 non-university clinics comprise 14% of the 43 Dutch hospitals with a full nephrology service in the Netherlands in 2004. The 3 university clinics represent 38% of 8 university clinics in the Netherlands.

Patient evaluation

Baseline measurements consisted of a questionnaire recording smoking behavior, physical activity and medication use. Physical examination consisted of measurement of height, weight and blood pressure (oscillometric blood pressure

measurements after 15 minutes of supine rest, mean of five measurements in the following fifteen minutes). Blood was drawn and a 24 hour urine sample was collected. Blood and urine samples were analyzed by the laboratory of the center. Medical history was obtained from the medical records. History of CV disease was defined as a history of myocardial infarction, stroke or vascular intervention. Diabetes mellitus was defined as the use of glucose lowering drugs or a fasting glucose >126 mg/dl (7.0 mmol/l). Adherence to the Dutch Guidelines of Healthy Physical exercise was determined with the validated SQUASH questionnaire.(14) The underlying diagnosis of kidney disease was determined by the treating physician and categorized using the ERA-EDTA (European Renal Association) registration criteria. Income was estimated from postal code area based upon data of Statistics Netherlands.(15) Presently, the MDRD formula is well accepted. To allow comparisons with other studies, we report eGFR using the abbreviated MDRD formula.(16)

Data analysis

Baseline characteristics were given for the study population by participating center and expressed as mean (SD) or proportions. Differences between centers in risk factors were studied using analysis of variance adjusted for age and gender if applicable. Mann Whitney U test was used when comparing two groups. For risk factors primarily treated by pharmacotherapy the presence of treatment was assessed. With regard to missing cases two analyses were performed: An analysis without cases with missing values was performed and an analysis, in which missing data was imputed. The presented data are after imputation.

Quality of Care score

Based on guidelines available at the time of inclusion (2004), eleven treatment goals proven or very likely associated with CV risk and risk of progression of kidney failure were defined as shown in Table 1.

Table 1: Goals and relevant guidelines for cardiovascular risk factors in MASTERPLAN

Risk factors	**Goal**	
Blood pressure	</= 130/85 mm Hg[a]	
Proteinuria		
Protein excretion in urine	< 0.5 g/day	
Lipids		
Fasting LDL[b]	< 2.6 mmol/l	
Anemia		
Hemoglobin concentration	> 6.8 mmol/l AND </= 7.4 mmol/l[c]	
Glucose		
Fasting glucose	< 7.0 mmol/l	
Non Fasting glucose	< 9.0 mmol/l	
Calcium/Phosphate metabolism		
Phosphate	</= 1.5 mmol/l	
PTH[d]	eGFR[e] > 30ml/min	< 7.7 pmol/l
	15-30 ml/min	7.7-12.1 pmol/l
	<15 ml/min	16.5-33 pmol/l
Healthy Nutrition		
Protein	0.8 –1.0 g /kg ideal bodyweight/ day	
Sodium excretion	100 mmol/24 hr	
Fat	Reduce fat, unsaturated fats preferred	
Energy	30-35 kcal/ kg ideal bodyweight/ day	
Overweight		
Body mass Index	<25 kg/m^2	
Physical activity	5x/week 30 minutes moderate activity	
Smoking	To Quit	

A: In case of proteinuria > 1g/day: 125/75 mm Hg; B: LDL = Low density lipoprotein; C: In case of erythropoiesis stimulating agent use; D: PTH = parathyroid hormone; E: eGFR= estimated Glomerular Filtration Rate

Achievement of a particular treatment goal was credited by 1 point. Thus, to each participant a maximal score of 11 points could be given. Quality of risk factor management was quantified as an unweighted summation of the score for these eleven goals. The calculated QoC score thus ranges from zero to 11.

An additional score was constructed which incorporated only the risk factors primarily treated by pharmacotherapy. This score was also unweighted and had a maximum of 7 points. Treatment for the different components of the QoC was defined as any drug specifically prescribed to treat this disorder. For proteinuria and BP any use of any antihypertensive medication was considered treatment.

Determinants of quality of care

Factors related to QoC were studied using univariable linear regression models. The factors evaluated were age, gender, race, prior CV disease, presence of diabetes mellitus, previous kidney transplant, eGFR, primary nephrological diagnosis (using congenital kidney disease as a reference) and treatment center. Center E was used as reference; this was the worst performing center with regard to unadjusted QoC score (Table 2).

Determinants that showed a univariable relationship with the QoC score with a *p*-value < 0.157 were entered in the multivariable linear regression model. This value is derived from prognostic modeling.(17) Since patients are clustered within hospitals and this might affect associations between QoC and its determinants, we applied generalized estimating equations (GEE) to correct for this clustering.(18) The analysis was done with SAS v9.1 (SAS institute inc., Cary, USA). Possible confounders (hospital size, academic status, no. of visits in the year prior to randomization, duration of follow-up by a nephrologist or internist prior to inclusion (this was recorded using the dates of the visits in the year prior to inclusion)) were studied separately univariable and in the constructed multivariable model.

Center performance with individual risk factors.

Performance of the different centers with regard to the defined eleven risk factors was plotted. The performance of centers was evaluated in a model adjusted for age, gender, cause of kidney disease, monthly income, kidney function, race and a history of kidney transplantation. Centers were also ranked by their adjusted QoC-scores and by the adjusted QoC-scores for the risk factors primarily treated by pharmacotherapy, to allow for easy comparison of both scores.

Results

Between April 2004 and December 2005, 793 prevalent patients were enrolled (65-105 patients/center). Five patients did not meet inclusion criteria (n=3) or declined participation after randomization (n=2). Data of 788 patients were available for analysis. These patients had been under medical specialist care for a median of 308 days (interquartile range = 233-361 days). Baseline characteristics of the entire cohort are presented in Table 2. There were significant differences in baseline characteristics between centers for all parameters except for prior CV disease, history of diabetes mellitus, estimated income, proteinuria, smoking and adherence to guidelines of physical activity (Table 2). Data on serum PTH-levels, proteinuria and sodium in urine were unavailable in respectively 4.1%, 5.3% and 8.5% of patients. No difference was seen between centers in the availability of data. Table 3 describes the overall performance for the individual treatment-goals, and their relation with pharmacotherapy. The percentage of patients on goal ranged from 17% to 92%. When considering achievement of treatment goals, hemoglobin ranked highest and urinary sodium excretion lowest. 37% of patients had adequately controlled blood pressure.

Table 2: Characteristics of study population in the participating centers (A – I).

	Total (n=788)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	***p*-value**
Age (years)	59(13)	54(13)	61(12)	59(12)	53(13)	60(13)	62(11)	67(13)	59(12)	60(12)	<0.001
Male sex	534(68%)	64%	76%	76%	68%	59%	77%	64%	55%	66%	0.012
Caucasian race	725(92%)	93%	95%	94%	99%	73%	95%	88%	95%	100%	<0.001
Kidney disease											<0.001
diabetic nephropathy	81 (10%)	9%	9%	4%	9%	12%	14%	18%	5%	16%	
renovascular	212 (27%)	6%	49%	15%	4%	43%	35%	42%	11%	38%	
GN	155 (20%)	20%	9%	18%	34%	17%	14%	11%	32%	24%	
IN	86 (11%)	13%	6%	6%	25%	11%	9%	9%	14%	3%	
congenital (including PKD)	94 (12%)	21%	7%	5%	20%	5%	8%	6%	24%	15%	
unknown	160 (20%)	31%	20%	52%	8%	12%	20%	14%	14%	4%	
Prior CV disease (myocardial infarction, stroke or intervention)	232 (29%)	29%	38%	30%	16%	29%	36%	30%	23%	34%	0.40
History of Diabetes Mellitus	179 (23%)	22%	22%	18%	21%	32%	28%	39%	14%	27%	0.10
Kidney transplant recipient	110 (14%)	32%	3%	10%	30%	14%	8%	3%	0%	21%	<0.001
Income (*1000euros)	1.9 [1.6/ 2.3]	1.8 [1.6/ 2.3]	1.8 [1.5/ 2.2]	1.9 [1.6/ 2.4]	2.0 [1.8/ 2.4]	1.9 [1.7/2.4]	1.8 [1.6/ 2.2]	1.7 [1.5/2.2]	1.8 [1.5/2.1]	1.9 [1.5/ 2.2]	0.42*
Estimated GFR (MDRD) (ml/min/1.73m^2)	37(14)	33(13)	37(15)	36(11)	40(13)	38(16)	44(16)	37(13)	34(11)	34(11)	<0.001
Creatinine (µmol/l)	182(68)	201(74)	186(68)	182(55)	168(53)	168(82)	160(58)	180(78)	191(74)	173(60)	0.002
Systolic BP (mm Hg)	135(20)	127(16)	145(22)	136(18)	128(16)	140(23)	140(19)	131(25)	128(19)	141(17)	0.001
Diastolic BP (mm Hg)	78(11)	75(8)	82(12)	80(10)	76(8)	77(11)	81(9)	72(10)	76(13)	83(11)	0.001
Proteinuria (g/24 hr)	0.3 [0.1/0.8]	0.4[0.2/0.9]	0.1[0.03/ 1.2]	0.3 [0.2/0.9]	0.6 [0.1/1.3]	0.2 [0.1/0.6]	0.1 [0.0/0.4]	0.3 [0.1/0.8]	0.3 [0.1/1.0]	0.3 [0.1/0.8]	0.10*
LDL-cholesterol (mmol/l)	2.8(0.9)	2.5(0.7)	2.6(0.8)	2.7(0.8)	3.0(0.9)	3.1(1.1)	2.7(0.9)	2.2(0.8)	2.7(0.7)	2.2(0.8)	0.001

	Total (n=788)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	***p*-value**
Hemoglobin (mmol/l)	8.2(1.0)	8.0(1.0)	8.3(1.1)	8.4(1.0)	7.7(1.0)	8.0(1.0)	8.7(0.8)	8.1(1.0)	8.1(0.9)	8.4(1.0)	0.001
Fasting glucose (mmol/l)	6.0(1.9)	6.0(1.9)	6.2(1.8)	5.8(1.0)	5.4(1.9)	6.9(3.2)	5.7(1.1)	6.4(1.7)	5.5(1.4)	5.8(1.6)	0.001
HbA1C (%)	6.1 (0.9)	5.9(0.7)	5.8(0.6)	5.8(0.5)	6.3(1.0)	6.3(1.2)	6.2(0.8)	6.9(0.9)	5,9(0.7)	6.1(0.9)	0.001
Phosporus (mmol/l)	1.1(0.2)	1.1(0.2)	1.0(0.2)	1.0(0.2)	1.1(0.3)	1.3(0.3)	1.0(0.2)	1.2(0.2)	1.2(0.2)	1.1(0.2)	0.001
PTH (pmol/l)	9 [5/15]	12 [7/17]	8 [5/13]	7 [4/12]	9 [6/15]	14 [9/24]	6 [4/11]	10 [5/14]	9 [5/14]	11 [7/15]	0.001
Urinary sodium excretion (mmol/ day)	149 [114/190]	139 [106/168]	156 [120/196]	158 [127/208]	160 [130/200]	128 [96/164]	145 [111/196]	131 [103/167]	146 [119/171]	164 [122/211]	0.001
BMI (kg/m^2)	27.1 (4.7)	26.1(4.6)	26.7(4.2)	28.6(4.5)	27.1(5.6)	27.2(5.3)	27.2(4.0)	27.6(5.1)	25.6(4.3)	27.3(4.0)	0.006
Smoking	164 (21%)	20%	25%	19%	14%	28%	25%	15%	25%	19%	0.14
Adheres to guidelines of healthy physical activity	451 (57%)	57%	55%	65%	63%	59%	61%	47%	53%	59%	0.52
Quality of care score	6.7(1.5)	6.9(1.6)	6.7(1.5)	6.8(1.6)	6.4(1.5)	5.9(1.4)	6.8(1.5)	6.3(1.7)	6.5(1.5)	6.4(1.3)	0.004
No. of drugs	5 [3/6]	4 [3/6]	5 [3/6]	4 [3/5]	4 [2/5]	6 [5/7]	4 [3/6]	5 [3/6]	4 [3/6]	5 [3/6]	0.004

Values given are mean (sd) or N (%) median [interquartile range].
GN=glomerulonephritis, IN= interstitial nephritis, PKD= polycystic kidney disease, MDRD=Modification of Diet in Renal Disease, BP = blood pressure, BMI =Body Mass Index, CV= cardiovascular.

Table 3: Achievement of treatment goals in CKD patients.

		On target	Not on target
	Overall	**% on target on pharmacotherapy**	**% not on target on pharmacotherapy**
BP	295 (37)	93	96
Proteinuria	587 (79)	94	96
LDL-cholesterol	374 (48)	79	55
Hemoglobin	726 (92)	11	37
HbA1C	675 (88)	12	76
Phosphorus	710 (90)	10	25
PTH	377 (52)	28	28
uNA	120 (17)		
BMI	260 (33)		
Adherent to Dutch physical activity guidelines	451 (57)		
Current not Smoking	624 (79)		

Values given as N (%) BP= blood pressure, PTH= parathyroid hormone, uNA= Urinary sodium excretion, BMI= Body mass index.

Four percent of patients with inadequately controlled blood pressure were untreated, whereas 45% and 72% of patients with increased levels of LDL-cholesterol and PTH were untreated.

Quality of care.

The mean QoC score for the entire cohort was 6.7 (±1.5) (Table 2). For the individual centers, the mean score ranged from 5.9 to 6.9. Only in 1.5% of patients a score of ten or eleven was found (Figure 1a). In 70% of patients a score of 7 or less was found.

The mean score for risk factors primarily treated by pharmacotherapy was 4.8 (±1.1) (Figure 1b).

Figure 1a: Distribution of quality of care, expressed as the sum of the achieved individual treatment goals for the entire study population. Eleven treatment goals were identified. The maximal score is 11.

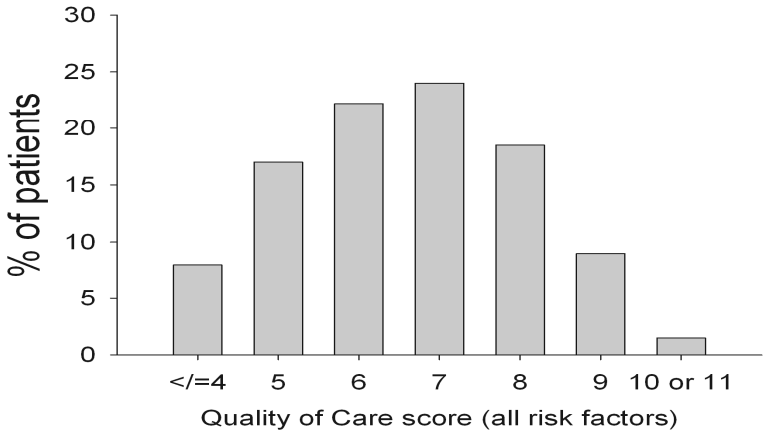
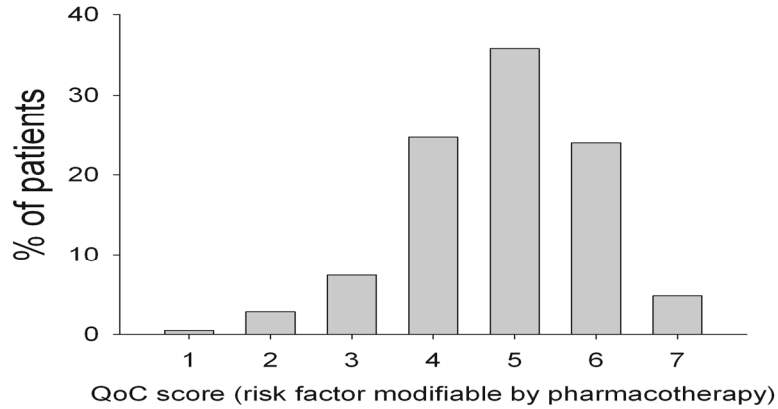


Figure 1b: Distribution of the QoC score based on 7 risk factors that are primarily treated by pharmacotherapy.



Determinants of quality of care.

Table 4 shows univariable and multivariable changes in QoC associated with a one unit change of the determinant. A negative regression coefficient is associated with a decline in QoC and a positive regression coefficient is associated with a rise in QoC. Kidney transplant recipients tended to have a lower QoC score, as did

patients with a history of DM, patients with diabetic nephropaty or renovascular disease .(Table 4) Higher eGFR, higher monthly income and Caucasian race were associated with a higher QoC score. As compared to center E other centers showed a significantly higher QoC in univariable analyses.(Table 4) The difference between centers persisted in generalized estimating equations analysis with adjustment for the mentioned determinants and additionally age and gender.(Table 4) The differences between treatment centers could not be explained by differences between the center size (number of beds/center (p=0.20)), the number of visits per patient in the year prior to randomization (p=0.19), the time a patient was seen by an internist or nephrologist prior to inclusion (p=0.18) or setting (university clinic versus non-university clinic (p=0.82)).

In additional analyses we observed that the QoC score was negatively associated with the number of drugs per patient. The QoC score decreased by 0.13 per drug added (p<0.001). However, addition of this variable in the multivariable model shown in Table 4 did not alter the results of our analysis (data not shown).

We performed similar analyses using a QoC score based on risk factors that are primarily treated by pharmacotherapy. Firstly, a ranking was performed based upon an adjusted calculated score for both QoC scores.(Table 5) In general the ranking seems more or less comparable for both scores, with the exception of center C, E and F.(Table 5)

In the multivariable analysis additional adjustment was made for lifestyle associated risk factors (GEE model 2, Table 5). Differences between centers were not influenced by this additional adjustment.

Table 4: Relation between quality of care, defined as the number of achieved treatment goals on target, with potential determinants.

	Univariable		Multivariable	
Determinant	**B**	**95%CI**	**B**	**95%CI**
Age (yr)	0.00	-0.01 to 0.01		
Male sex	-0.17	-0.40 to 0.06	-0.21	-0.40 to -0.03
Caucasian race	0.70	0.30 to 1.09	0.57	0.06 to 1.08
Prior CV disease	-0.16	-0.40 to 0.08		
History of DM	-0.75	-0.99 to -0.50	-0.27	-0.62 to 0.08
Kidney transplant recipient	-0.27	-0.58 to 0.04	-0.46	-0.67 to -0.25
Income (/1000 euro/ month)	0.22	0.05 to 0.38	0.23	0.12 to 0.33
eGFR (MDRD) (ml/min/1.73m^2)	0.02	0.02 to 0.03	0.02	0.01 to 0.04
Kidney disease				
diabetic nephropathy	-1.41	-1.85 to -0.96	-1.06	-1.70 to -0.41
renovascular	-0.54	-0.90 to -0.17	-0.49	-0.92 to -0.06
GN	-0.43	-0.81 to -0.04	-0.35	-0.79 to 0.09
IN	-0.46	-0.90 to -0.02	-0.28	-0.60 to 0.04
congenital (including PKD)	*			
unknown	-0.19	-0.58 to 0.19	-0.32	-0.71 to 0.06
Treatment center				
A	0.79	0.36 to 1.21	0.70	0.49 to 0.91
B	0.54	0.12 to 0.96	0.34	0.20 to 0.48
C	0.40	0.23 to 1.07	0.47	0.22 to 0.73
D	0.25	-0.17 to 0.67	-0.05	-0.29 to 0.18
E	**			
F	0.76	0.34 to 1.19	0.40	0.19 to 0.60
G	0.22	-0.25 to 0.69	0.16	0.05 to 0.26
H	0.76	0.29 to 1.23	0.47	0.28 to 0.67
I	0.57	0.11 to 1.04	0.50	0.36 to 0.65

B = the unstandardized regression coefficient; it shows the absolute change of the quality of care score associated with a one unit increase of the determinant (e.g. being male is associated with a reduction of the quality of care score with 0.17 (95% CI = -0.40 to 0.06), 95%CI = 95% confidence interval, CV=cardiovascular (myocardial infarction, stroke or intervention), DM=diabetes mellitus, eGFR=estimated glomerular filtration rate, MDRD=Modification of Diet in Renal Disease, GN=glomerulonephritis, IN= interstitial nephritis, PKD= polycystic kidney disease

* used as a reference kidney disease for the analyses.

** used as reference center for the analyses.

Table 5: Adjusted score and ranking of centers for both the QoC based on all risk factors and a score for QoC based on risk factors primarily treated by pharmacotherapy. The latter score was evaluated in multivariable analysis without and with adjustment for lifestyle-factors.

Center	Total		Pharmacotherapy only		GEE Model 1		GEE Model 2	
	Adjusted score	Rank	Adjusted score	Rank	B	*p* value	B	*p* value
A	7.0	1	5.2	1	0.7	<0.001	0.7	<0.001
B	6.7	6	4.9	5	0.4	<0.001	0.4	<0.001
C	6.8	3	4.8	6	0.3	<0.001	0.3	<0.001
D	6.3	9	4.6	8	0.1	0.12	0.1	0.10
E	6.4	8	5.0	3	0.5	<0.001	0.5	<0.001
F	6.8	3	4.7	7	0.1	<0.001	0.2	<0.001
G	6.6	7	4.5	9	Ref			
H	6.9	2	5.0	3	0.5	<0.001	0.5	<0.001
I	6.8	3	5.2	1	0.7	<0.001	0.7	<0.001

An adjusted score was calculated with adjustment for: for age, gender, race, history of CV disease, cause of kidney disease, prior kidney transplantation, history of diabetes mellitus, monthly income and eGFR. Centers were ranked according to their adjusted score: the center with the highest score is ranked as one.
GEE = generalized estimating equations were performed
Model 1: adjusted for age, gender, race, history of CV disease, cause of kidney disease, prior kidney transplantation, history of diabetes mellitus, monthly income and eGFR.
Model 2: Model 1 + BMI, sodium excretion in urine, smoking, physical activity

Center performance with individual risk factors.

Figure 2 illustrates the QoC in the centers for the individual treatment parameters, expressed as the percentage of patients that achieved the target. The absolute difference between the best and worst performing center based on the baseline data of the study for a risk factor ranges from 14% for smoking (on target range 72% - 86%) to 50% for PTH (on target range 30% - 80%). The mean difference for lifestyle modifiable risk factors (smoking, body mass index, urinary sodium excretion, physical activity) was 19% versus a mean difference of 32% for pharmacotherapy modifiable risk factors (BP, proteinuria, phosphate, PTH, Hba1c, Hb) (p=0.04).

Logistic regression with adjustment for age, gender, race, history of CV disease, cause of kidney disease, prior kidney transplantation, history of diabetes mellitus and eGFR showed significant differences between centers ($p<0.02$) for phosphate, hemoglobin, Hba1c, PTH, LDL cholesterol, blood pressure, BMI and urinary sodium excretion, no significant differences were observed for proteinuria, physical activity and smoking.

Discussion

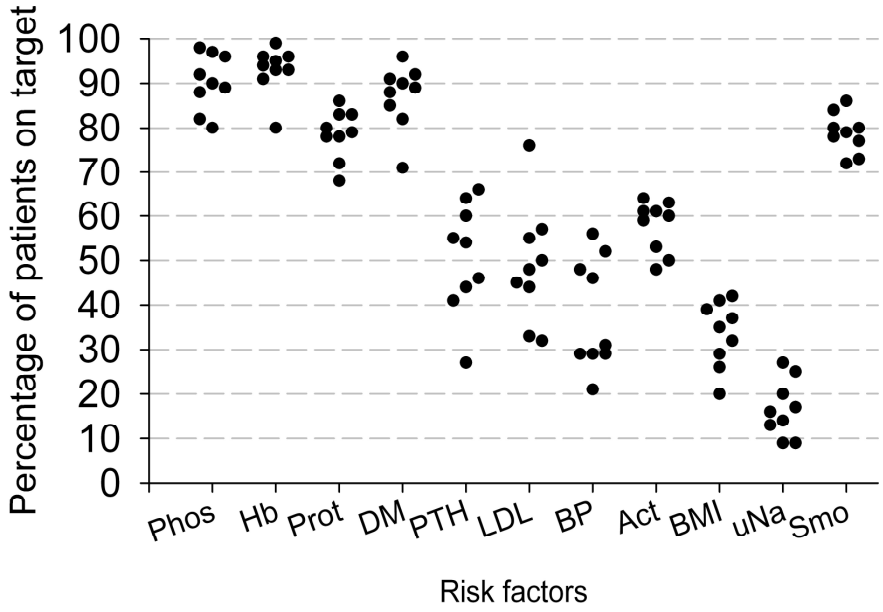
Our study clearly indicated indicated that in a considerable percentage of patients with mild to moderate CKD, treatment goals aimed at reducing risk of kidney failure progression and reducing CV morbidity were not achieved. This conclusion held for risk factors related to lifestyle and to pharmacotherapy. Importantly, there were differences between the centers that persisted after adjustment for a variety of determinants including differences in patient mix between centers. Therefore, this finding may point to center specific causes that need further study in order to improve the QoC.

Quality of care.

Based upon the QoC score (Figure 1a) and the performance with individual risk factors (Figure 2) it was evident that treatment goals were very often not achieved in this cohort. Our data are in line with previous studies in patients with CKD, that all showed an inadequate control of risk factors in patients with CKD.(7-9) Moreover, when comparing these studies it is clear that despite the recent introduction of guidelines on risk factor management in patients with CKD, there was only little improvement over the last decade.

Figure 2: Performance of nine centers in eleven risk factors.

In the figure for every risk factor per center the percentage of patients achieving the treatment goal is depicted after adjustment for age, gender, race, history of CV disease, cause of kidney disease, prior kidney transplantation, history of diabetes mellitus, monthly income and eGFR.
Phos = serum phosphorus, Hb = hemoglobin, Prot = proteinuria, DM = diabetes mellitus, PTH= parathyroid hormone, LDL = ldl-cholesterol, BP = blood pressure, Act = physical activity, BMI = body mass index, uNa= urinary sodium excretion, Smo = smoking



This is most clearly illustrated by the blood pressure data. Tonelli reported an achieved mean blood pressure of 141/78 mmHg in a population of 304 Canadian CKD patients evaluated in 1999, de Nicola in a cohort of 1058 Italian patients with CKD stage 3-5 evaluated in 2000-2003 reported 140/80 mmHg in, and the mean value in our study was 135/78 mmHg.(7;8) Admittedly, this might be explained by a difference in methods of blood pressure assessment (office blood pressure in previous studies versus automated device in our study), in risk factor management between countries and more strict treatment goals in newer guidelines.(9;11;19)

We observed a large variation in the quality of control of risk factors that are treatable by pharmacotherapy, i.e. blood pressure, lipids, and PTH (Figure 2). Whereas most patients received some form of antihypertensive treatment, many patients with inadequately controlled cholesterol and PTH levels were untreated. Similar observations have been made by Tonelli et al.: patients with CKD were less likely to receive pharmacotherapy for dyslipidemia or anemia, whereas most were treated for high blood pressure.(7)

Determinants of quality of care.

Several patient-related factors were related to the level of QoC. Our findings that a decline in kidney function was related to a lower QoC score was in agreement with others and has several explanations.(7;8) It could be attributed to the fact that some risk factors occurred during the course of kidney failure progression and were not apparent in the early stages of CKD (for instance anemia and hyperphosphatemia).(8) Secondly, some risk factors become more difficult to control as kidney failure progresses (for instance blood pressure). Furthermore literature data suggests that in CKD physician's focus may be predominantly on risk factors for kidney disease progression (hypertension, proteinuria), with less attention for CV risk factors such as cholesterol.(7) We confirmed this observation: more patients received pharmacotherapy for hypertension than for dyslipidemia in our cohort.

In agreement with other studies, diabetic nephropathy, gender and race were associated with a worse control of risk factors.(20;21) In our study age, a variable predictive in studies in coronary heart disease patients, was not associated with QoC.(21;22)

An additional observation which should be addressed is the apparent paradoxical relation between number of prescribed drugs and QoC-score. It is counterintuitive

that more drugs are associated with less achievement of treatment-goals. We interpret this finding as a confounder: confounding by indication in particular. The worse controlled patient was prescribed more drugs in an effort to improve outcome. In the absence of achieving the treatment-goal this will result in the association established in our cohort.

Possibly the most important finding of our analysis was that treatment center was an independent and considerable determinant of QoC. The multivariable adjusted difference between the highest and lowest ranking center in number of risk factors not on target was as high as 0.75. To put this into perspective: the same difference existed between patients with an eGFR of 30 and 60 ml/min/1.73m^2 respectively. A difference that was clearly associated with an increase of CV risk.(23) Few data are available on differences in the QoC between countries, between regions and between hospitals.(9-11) Differences have partly been attributed to the size of the hospital, the role of the hospital as teaching hospital and to some financial incentives. We were not able to confirm these findings.
It was not clear which factors may explain the observed differences. Obviously, we could not exclude that undetermined patient characteristics, such as (un)employment or social economic status were important. Generally, patients with low education and socio-economic status are more likely to have lower scores on lifestyle modifiable factors.(24) In these patients undertreatment is suspected to be caused by the inability to pay for the additional costs of medication. In the Netherlands all patients have health care insurance and receive (most of) the prescribed medication free of charge. There is also no difference in the availability of care for patients based upon socio-economic factors or type of insurance. All hospitals in the Dutch healthcare system are equally accessible for all patients. Moreover, our analysis showed that all centers perform more or less equal for

lifestyle factors. The most important differences between centers concerned pharmacotherapy modifiable risk factors. This suggests not only that socioeconomic status is not a major factor but also that improvement of QoC is indeed feasible. This finding was supported by the fact that additional adjustment for lifestyle factors (smoking, urinary sodium excretion, BMI and physical activity) in the model for QoC score based on risk factors that were primarily treated by pharmacotherapy, did not markedly affect the differences between centers.
This suggested that not only unmeasured patient-characteristics but also treatment-related factors might explain the observed center difference. It was also evident that the difference between the centers was not the result of overall variation in performance of the physicians that take care of the patients. Performance for one risk factor was not related to performance in another factor. The observation that the differences in quality of control were larger for pharmacotherapy modifiable risk factors than for lifestyle modifiable risk factors supported the idea of real treatment-differences between centers.
We could only speculate what explains the unexpected differences between centers. There may be differences between physicians in their choice of target, some putting more emphasis on regulating blood pressure, others focusing on phosphorus and PTH. There may be a difference in therapeutic inertia (i.e. the tendency not to adjust the intensity of treatment, despite the fact that a certain risk factor does not meet the treatment goal). Also differences in therapeutic strategy may be involved. For instance, drug dosing or the combination of certain drugs (e.g. antihypertensives) might affect the number of treatment goals on target. Future research taking into account aforementioned aspects of treatment should identify the causes of these differences.

Limitations of the analysis.

The current analysis has several limitations. This analysis was performed using the baseline data of patients who were included in a prospective randomized trial. Information on non-participating patients who fulfilled the inclusion criteria was lacking, therefore we could not exclude that the differences between centers are partly explained by differences in their selection of patients.

The observed difference between centers was an unexpected finding; therefore we also lacked information on the attitude of the physicians with respect to guidelines and the defined treatment-targets. Information on dosage of drugs was not included in our data-analysis.

In our analysis we constructed a score in which every risk factor had the same weight. One could argue that a weighted score taking into account the size of contribution to CV risk would result in a more meaningful score. However, currently there are virtually no data to estimate these risks accurately. Therefore, we decided not to add weight to the different risk factors. Additionally the role of every separate risk factor in the score could be questioned. The current score is composed of risk factors which are extensively addressed in international guidelines primarily focused at the reduction of CV events and consolidation of kidney function and therefore comprise a good overview of targets of treatment in patients with CKD. Particularly lipid lowering therapy might be considered debatable. At the time of start of the study major lipid lowering trials in dialysis patients however were not yet published.(25;26) Moreover the available data supported the hypothesis of cardiovascular protection of statins in CKD.(27) However, the score has not been validated in prospective studies and still has to prove its value with regard to hard endpoints like myocardial infarction, death or kidney disease progression.

Ideally, QoC should only take into account patients who originally had abnormal values. In that case, analysis of a change over time more adequately reflected the performance of the center or physician. The present cross sectional study did not allow such an analysis.

It is important to realize that we reported on a Dutch population primarily under the care of nephrologists. This notion did not affect the established center-effect, but might effect generalizability of the findings. This may have had two consequences. Firstly, patients under care of a nephrologist are a different population than patients under care of an internist or general practitioner. It is likely that more polycystic kidney disease and glomerulonephritis are present in this group. Furthermore, diabetes is less prevalent in the Dutch general and dialysis population compared to other countries and therefore it is likely that this also holds for the CKD population.(28;29)

Conclusion

In CKD patients, risk factors for kidney failure progression and CV morbidity and mortality were inadequately controlled. Many patients did not receive appropriate pharmacotherapy, indicating that QoC can be improved. Treatment center proved to be an important determinant of the QoC score. The difference between centers was not explained by patient characteristics or readily identifiable hospital characteristics. There was no uniform ranking of hospitals when considering the individual risk factors. These data suggests that physician's interest and preference may be important determinants of QoC. This is a potentially modifiable determinant of the quality of patient care.

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Chapter 2.2

Hospital specific factors affect quality of blood pressure treatment in Chronic Kidney Disease.

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Abstract

Background

Blood pressure (BP) is the most important modifiable risk factor for cardiovascular (CV) disease and progression of kidney dysfunction in patients with chronic kidney disease. Despite extensive antihypertensive treatment possibilities, adequate control is notoriously hard to achieve. Several determinants have been identified which affect BP control.

In the current analysis we evaluated differences in achieved BP and achievement of the BP-goal between hospitals and explored possible explanations.

Methods

At baseline BP was measured in supine position with an oscillometric device in 788 patients participating in the MASTERPLAN study. We also retrieved the last measured office-BP from the patient records. Additional baseline characteristics were derived from the study-database. Univariate and multivariate analyses were performed with general linear modeling using hospital as a random factor.

Results

In univariate analysis hospital was a determinant of the level of systolic and diastolic BP at baseline. Adjustment for patient, kidney disease, treatment or hospital characteristics affected the relation. Yet, in a fully adjusted model differences between centers persisted with a range of 15 mmHg for systolic BP and 11 mm Hg for diastolic BP.

Conclusion

Despite extensive adjustments a clinically relevant, statistically significant difference between hospitals was found in standardized BP measurements at baseline of a randomized controlled study. We hypothesize that differences in the approach towards BP control exist at the physician level and explain these differences between hospitals.

Introduction

Blood pressure (BP) is considered to be the most important modifiable cardiovascular (CV) risk factor. In large population studies a reduction of systolic BP of 20 mm Hg is associated with a 33% reduction in stroke and ischemic heart disease in patients aged 80-89 years and an even greater reduction of 62% in stroke and 51% in ischemic heart disease in those aged 50-59 years.(1) The prevalence of hypertension is high in patients with chronic kidney disease (CKD) and increases with CKD stage from 79% in CKD stage I to 95% in CKD stages IV and V.(2) In patients with CKD, reduction of BP is not only important to prevent CV events but also to attenuate the decline of kidney function.(3;4)

Nowadays, physicians can use a multitude of effective BP lowering agents and, in addition, focus on lifestyle changes. Despite this armamentarium, the large majority of patients does not achieve treatment-goals.(5-7) Several factors have been identified to be associated with poor BP control, including more advanced kidney dysfunction, poor adherence, absence of health insurance and physicians not adhering to guidelines or showing therapeutic inertia.(8-11)

Recently, we reported in CKD patients that the hospital where a patient receives treatment was independently associated with a quality of care score based on 11 different risk factors.(12) In the current analyses, we evaluated the BP and the

degree that BP-goals were achieved, compared results between centers and explored possible explanations for the observed differences.

Subjects and Methods

MASTERPLAN study

The MASTERPLAN study [Trial registration ISRCTN registry: 73187232 (http://isrctn.org)] is a randomized controlled trial conducted in nine hospitals with a nephrology department in the Netherlands. Rationale and design have been published elsewhere.(13;14) Ethical approval was given by the ethics board of the University of Utrecht with additional endorsement of local applicability by the ethical boards of each of the participating hospitals.

Subjects: In brief, adult patients with CKD (estimated GFR between 20 – 70 ml/min) were included in the study.

The effects of a multitargeted treatment regimen executed by a specialized nurse under the supervision of, and in collaboration, with a nephrologist are compared with the care delivered by the patient's own physicians, also mostly nephrologists. In both arms of the study, the same sets of guidelines apply. The primary end point is a composite of fatal and nonfatal myocardial infarction, stroke and cardiovascular mortality. Secondary end points are all-cause mortality, achievement of treatment goals for the various risk factors, decline of kidney function and quality of life. Follow-up will continue for five years. The study was approved by an institutional review committee and all subjects gave informed consent.

All participating hospitals are teaching hospitals that offer a full range of nephrology treatment including kidney replacement therapy (both haemodialysis and peritoneal dialysis) and are involved in the care of kidney transplant

recipients. Three hospitals are university clinics that offer tertiary care and have kidney transplant programs. The number of beds per hospital ranges from 414 to 953.

Patient evaluation

Baseline measurements consisted of a questionnaire to obtain information on smoking behavior, physical activity and medication use. Physical examination consisted of measurement of height, weight and BP (oscillometric BP measurements after 15 minutes of supine rest, mean of five measurements in the following fifteen minutes). BP was concluded to be on target if oscillometric BP level was ≤ 125/80 mmHg in patients without proteinuria and ≤ 120/70 mmHg in patients with ≥ 1 gr proteinuria / 24 hr (guidelines indicate goals of 130/85 and 125/75 mmHg respectively for office measurement; an additional 5 mmHg adjustment for both systolic and diastolic BP is applied for the period of supine rest and use of an oscillometric device).(15;16) Also the BP of the patient measured during the last outpatient visit prior to randomization (screening visit) was retrieved. These were sphygmomanometric office measurements usually taken in sitting position during the visit in all centers taken by an experienced internist. The sphygmomanometric devices were of the aneroid mechanical type.
All devices (both oscillometric and sphygmomanometric) are validated annually in participating centers. Aneroid devices were validated by local technical services in the respective centers. Most centers retained a mercury sphygmanometer in their technical department to allow for correct validation. Additional validation prior to start of the study of the oscillometric devices was performed. This was added to the methods section. Per center different types of oscillometric devices are used: BP100 (Gambro, Lund, Sweden), Critikon (Critikon, Tampa, Florida), Dinamap procare (GE Medical Systems Information Technologies Inc.,

Milwaukee, Wisconsin), Accuratorr plus (Datascope, Mahwah, New Jersey). Blood was drawn and a 24 hour urine sample was collected. Blood and urine samples were analyzed by the laboratory of the center. Medical history was obtained from the medical records. History of CV disease was defined as a history of myocardial infarction, stroke or vascular intervention. Diabetes mellitus at baseline (DM) was defined as the use of glucose lowering drugs or a fasting glucose >126 mg/dl (7.0 mmol/l). Adherence to the Dutch Guidelines of Healthy Physical exercise was determined with the validated SQUASH questionnaire.(17) The underlying diagnosis of kidney disease was determined by the treating physician and categorized using the ERA-EDTA (European Renal Association) registration criteria. To allow comparisons with other studies, we report eGFR using the abbreviated MDRD formula.(18)

Data analysis

Baseline characteristics were given for the study population by participating hospital and expressed as means (SD) or proportions. For non-parametric data medians [range] were supplied. Differences between centers in risk factors were studied using analysis of variance adjusted for age and gender if applicable.

With regard to missing data two analyses were performed: One complete case analysis (all complete data) and one, in which missing data were imputed. The presented data are based on imputed data. Five separate imputations were performed and analyses were performed on each imputation separately.(19) Results were then pooled via the statistical software (SPSS 17).

Since patients cluster within hospitals, we applied for continuous dependent variables general linear modeling and included hospital as a random effect.(20) As a measure for the explanation of the variability in the model η^2 is used, since for this type of analysis η^2 is considered more appropriate than R^2.

For multivariate analyses of the center effect different models have been constructed. Based upon known determinants of systolic and diastolic BP, both from literature and our own analyses we came to the following models:

Model 0: no adjustment;

Model 1(patient characteristics): age, gender, race, history of CV disease, history of DM, Body Mass Index (BMI), income, current smoking, physical activity, left ventricular hypertrophy on ECG;

Model 2 (additional kidney disease characteristics): Model 1 + diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium;

Model 3 (additional treatment characteristics): Model 2 + sodium excretion in urine, no. of visits in the year prior to randomization, no. of antihypertensives, RAS intervention (use of either an Ace-inhibitor or an angiotensin receptor blocker), use of diuretics;

Model 4 (additional hospital characteristics): Model 3 + hospital size, academic status.

Adjusted means were calculated for systolic and diastolic BP measured at baseline and at the screening visit. Adjustment was performed for: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG, nephrological diagnosis, history of kidney transplantation, eGFR, proteinuria, sodium excretion in urine, no. of visits in the year prior to randomization, no. of antihypertensives, RAS intervention, use of diuretics and hospital size. The analyses were performed with SPSS 17.0 (SPSS inc., Chicago, USA).

Results

793 patients were included in the study between April 2004 and December 2005. Three patients did not meet inclusion criteria and two patients withdrew consent directly after randomization, leaving 788 patients available for the analyses. Baseline characteristics are given in Table 1. The majority of patients are male (68%) and Caucasian (92%). Mean BP is 135 (±20)/78 (±11) mm Hg. The proportion of patients considered to have achieved the treatment goals based on the oscillometric BP measurement is 28%, varying between centers from 12%-42%. (Table 1)

Differences in BP between hospitals

In the general linear modeling analysis with center as a random factor systolic BP was significantly lower in all hospitals compared to the reference center (Center B). (Table 2a)

Model 1 and 2 showed that some of the differences are explained by respectively patient and kidney disease related characteristics. (Table 2a) Factors added in models 3 and 4 did not seem to contribute much. For diastolic BP patient related characteristics (Model 1) have the greatest contribution. Adjustment for pharmacotherapy (i.e. the use of renin angiotensin system (RAS) intervention (i.e. use of either an ACE inhibitor or angiotensin receptor blocker) or diuretics, did not explain the differences between hospitals (Model 3).

In the final full multivariate model (Model 4) a clear center effect remained present, i.e. hospitals A, C, D, G and H showed significant lower systolic BP levels compared to the reference center. The center effect explained about half of the variability that can be explained by the regression model; η^2 for the full model is 0.21 and 0.10 for the model without adjustments. Also in a reverse fashion for the

fully adjusted model without center η^2 was 0.13, whereas the fully adjusted model with center had a η^2 of 0.21. The range of the differences in adjusted systolic BP between hospitals was 15 mmHg.

For diastolic BP a center effect was found with center I having the highest diastolic BP and center G the lowest. (Table 1) After adjustment for additional determinants the differences remained. The difference between highest and lowest diastolic BP after adjustment is 11 mmHg. Hospital A, D, E and G also had a significantly lower diastolic BP compared to hospital F and I. (Table 2b).

Differences in oscillometric and sphygmomanometric (office) BP measurements

Based on the previous findings we performed additional analyses to explore the following issues as potential explanations of these findings.

1. Are there not only center differences in the oscillometric BP measurements (BP obtained with the BP measuring device at baseline of the study), but also in the sphygmomanometric BP measurements performed at the outpatient clinics during the last visit prior to entry into the study (median 32 days before inclusion (IQR 20-53 days). Figure 1 shows that on average oscillometric BP is lower than office BP (p=0.05 for systolic BP en p=0.006 for diastolic BP). Yet, the center effect remained present in both methods of BP assessment.

2. Do hospital differences disappear above a certain level of achieved BP goals? Such a finding might be interpreted as indicating that different targets are used in the hospitals. Figure 2 shows percentages of patients achieving treatment goals per center for three separate goals: a goal of 125/80 mmHg (120/70 mmHg if proteinuria > 1g/day) for oscillometric BP, a goal of 130/85 mmHg (125/75 mmHg if proteinuria > 1 g/day) for sphygmomanometric office BP, and a goal of 140/90 mmHg for sphygmomanometric office BP (independent of proteinuria).

Table 1: Baseline characteristics of the Masterplan cohort.

Variable	Total (n=788)	A (n=94)	B (n=100)	C (n=100)	D (n=100)	E (n=104)	F (n=91)	G (n=66)	H (n=65)	I (n=68)
Age (years)	59.1 (13.0)	54.3 (13.2)	60.9 (11.6)	59.3 (11.8)	52.5 (12.6)	59.9 (13.2)	61.9 (10.5)	66.9 (12.6)	58.5 (14.3)	60.3 (12.2)
Gender (male %)	68	64	76	76	68	59	77	64	55	66
Caucasian (%)	92	93	95	94	99	73	95	88	95	100
KTR (%)	14	32	3	10	30	14	8	3	0	21
Prior CV disease (%)	29	29	38	30	16	29	36	30	23	34
Cause of kidney disease (%)										
Unknown	20	31	20	52	8	12	20	14	14	4
Glomerulonephritis	15	16	6	17	31	14	7	8	14	22
Interstitial	9	11	5	6	23	8	4	5	11	3
Cystic	10	18	7	5	13	4	8	6	20	12
Other cong	2	3	0	0	7	1	0	0	5	3
Renovascular	27	6	49	15	4	43	35	42	11	38
Diabetes	10	9	9	4	9	12	14	18	5	16
Other multisyst	5	4	3	1	3	4	8	3	19	2
Other	2	2	1	0	2	4	4	5	3	0
BMI (kg/m^2)	27.1 (4.7)	26.1 (4.6)	26.7 (4.2)	28.6 (4.5)	27.1 (5.6)	27.2 (5.3)	27.2 (4.0)	27.6 (5.1)	25.6 (4.3)	27.3 (4.0)
Oscillometric BP (mmHg)	135(20)/78 (11)	127(16)/75 (8)	145(22)/82 (12)	136(18)/80 (10)	128(16)/76 (8)	140(23)/77 (11)	140(19)/81 (9)	131(25)/72 (10)	128(19)/76 (13)	141(17)/84 (11)
Office BP (mmHg)	137(20)/79 (10)	132(17)/82 (9)	145(23)/81 (8)	138(23)/80 (11)	135(15)/79 (7)	134(20)/79 (11)	139(23)/78 (11)	135(23)/73 (12)	134(19)/79 (10)	138(16)/80 (8)
No. of visits in year prior to inclusion	3 [0-31]	3 [1-31]	2 [0-5]	3 [1-8]	4 [2-31]	3 [0-8]	3 [0-8]	3 [0-8]	3 [0-10]	3 [1-8]
Creatinine (μmol/l)	182(68)	201(74)	186(68)	182(55)	168(53)	168(82)	160(58)	180(78)	191(74)	173(60)
eGFR (ml/min/1.73 m2)	37 (14)	33 (13)	37 (15)	36 (11)	40 (13)	38 (16)	44 (16)	37 (13)	34 (11)	34 (10)
Proteinuria (mg/24 hr)	300 [0-9300]	400 [100-9300]	163 [0 – 7000]	300 [20-7400]	600 [0 – 6640]	221 [0 – 9000]	100 [0 – 3700]	300 [0 – 6800]	400 [30-7000]	305 [0 – 6300]
Urinary sodium excretion (mmol/24 hr)	150 [29-419]	139 [29 – 261]	158 [57-283]	162 [51 – 419]	160 [46 – 340]	129 [31-343]	148 [44 – 297]	130 [34 - 279]	148 [48 – 318]	163 [48-366]

Variable	Total (n=788)	A (n=94)	B (n=100)	C (n=100)	D (n=100)	E (n=104)	F (n=91)	G (n=66)	H (n=65)	I (n=68)
Serum potassium (mmol/l)	4.4 (0.6)	4.5 (0.6)	4.5 (0.6)	4.2 (0.5)	4.7 (0.6)	4.7 (0.5)	4.3 (0.5)	4.3 (0.6)	4.5 (0.6)	4.4 (0.5)
LVH on ECG (%)	15	21	13	22	10	21	11	9	5	13
Income (*1000euros)	1.9 [1.6/ 2.3]	1.8 [1.6/ 2.3]	1.8 [1.5/ 2.2]	1.9 [1.6/ 2.4]	2.0 [1.8/ 2.4]	1.9 [1.7/2.4]	1.8 [1.6/ 2.2]	1.7 [1.5/2.2]	1.8 [1.5/2.1]	1.9 [1.5/ 2.2]
Physical activity (met/minxmin/week)	5190 [80-41940]	6460[240-21480]	4020[600-17340]	6420[600-17340]	5430[800-19765]	4690[120-16380]	4920[300-18300]	4400[80-28560]	4974 [120-16800]	6000[240-41940]
Smoking (%)	21	19	24	18	14	28	24	15	26	19
No. antihypertensives	2.4 (1.3)	2.3 (1.0)	2.6 (1.5)	2.4 (1.3)	2.1 (1.2)	2.5 (1.3)	2.4 (1.4)	2.4 (1.4)	2.2 (1.3)	2.5 (1.2)
RAS-intervention (%)	79	89	83	64	78	84	85	80	79	71
Beta-blocker (%)	50	37	57	63	57	45	43	39	42	62
CCB (%)	35	21	47	31	25	39	46	36	32	38
Diuretics (%)	50	60	45	56	37	56	40	53	46	60
Alfa-blockers (%)	9	3	15	7	1	17	11	8	8	10
Other antihypertensives (%)	1	0	1	3	1	1	2	0	0	0

Values given are mean (sd) or % or median [range].
KTR = kidney transplant recipient, CV = cardiovascular, GN = glomerulonephritis, IN = interstitial nephritis, PKD = polycystic kidney disease, BP = blood pressure, BMI = Body Mass Index, Oscillometric BP = oscillometric assessment after 30 min of supine rest, Office BP = sphygmomanometric BP during the last outpatient clinic prior to randomization, eGFR = estimated glomerular filtration rate by MDRD formula, RAS intervention= use of either an Ace-inhibitor or an angiotensin receptor blocker, CCB= Calcium Channel Blocker

Table 2a: Univariate and multivariate general linear modeling for systolic BP with hospital as a random effect.

Center	**Model 0: η^2=0.10**		**Model 1: η^2=0.17**		**Model 2: η^2=0.20**		**Model 3: η^2=0.21**		**Model 4: η^2=0.21**		
	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	95% CI
A	-18	<0.001	-15	<0.001	-15	<0.001	-13	<0.001	-13	<0.001	-19;-8
B	Ref		Ref		Ref		Ref		Ref		
C	-9	0.001	-9	<0.001	-8	0.004	-8	0.004	-8	0.004	-13;-2
D	-17	<0.001	-12	<0.001	-11	<0.001	-10	0.001	-10	0.001	-15;-4
E	-6	0.04	-6	0.02	-6	0.02	-4	0.11	-4	0.11	-9;1
F	-5	0.06	-6	0.04	-3	0.18	-3	0.20	-3	0.20	-9;2
G	-15	<0.001	-16	<0.001	-16	<0.001	-15	<0.001	-15	<0.001	-21;-9
H	-17	<0.001	-13	<0.001	-12	<0.001	-11	<0.001	-11	<0.001	-17;-5
I	-4	0.19	-3	0.30	-4	0.20	-3	0.30	-3	0.30	-9;3

Model 0: no adjustment
Model 1: patient characteristics: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, left ventricular hypertrophy on ECG.
Model 2: Model 1 + kidney disease specific: diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium.
Model 3: Model 2 + treatment related: sodium excretion in urine, no. of visits in the year prior to randomization, no. of antihypertensives, use of renin angiotensin modulating drugs, use of diuretics.
Model 4: Model 3 + center related: center size, academic status.
η^2 = is a measure of effect size for use in ANOVA, B = unstandardized regression coefficient (representing difference in BP in mm Hg with center B), *p* = *p*-value in statistical analysis.

Figure 1: adjusted BP values in different centers.
● = systolic oscillometric BP; o = diastolic oscillometric BP; ▼ = systolic office BP; Δ = diastolic office BP; ⊤ = 1 standard error of the mean; R = reference center.
Adjustment for: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG, nephrological diagnosis, history of kidney transplantation, eGFR, proteinuria, sodium excretion in urine, no. of visits in the year prior to randomization, no. of antihypertensives, use of ACEs or ARBs, use of diuretics and center size.

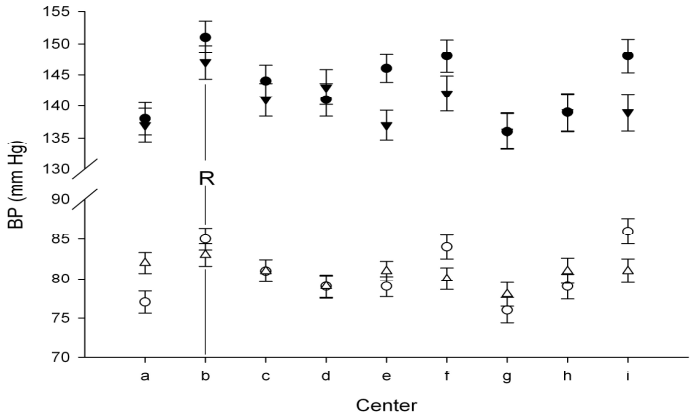

Table 2b: Univariate and multivariate general linear modeling for diastolic BP with hospital as a random effect.

Center	**Model 0: η^2=0.10**		**Model 1: η^2=0.17**		**Model 2: η^2=0.19**		**Model 3: η^2=0.19**		**Model 4: η^2=0.19**		
	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	95% CI
A	-7	<0.001	-8	<0.001	-8	<0.001	-8	<0.001	-8	<0.001	-11;-5
B	Ref		Ref		Ref		Ref		Ref		
C	-3	0.08	-4	0.05	-4	0.003	-4	0.007	-4	0.007	-7;-1
D	-6	<0.001	-7	<0.001	-7	<0.001	-7	<0.001	-7	<0.001	-10;-3
E	-5	<0.001	-6	<0.001	-5	<0.001	-5	0.001	-5	0.001	-8;-3
F	-1	0.49	-1	0.31	-1	0.66	-1	0.72	-1	0.72	-3;2
G	-11	<0.001	-10	<0.001	-10	<0.001	-9	<0.001	-9	<0.001	-13;-6
H	-6	<0.001	-5	0.001	-6	0.001	-5	0.001	-5	0.001	-9;-2
I	1	0.49	1	0.84	1	0.44	2	0.33	2	0.33	-2;5

Model 0: no adjustment
Model 1: patient characteristics: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity.
Model 2: Model 1 + kidney disease specific: diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium.
Model 3: Model 2 + treatment related: sodium excretion in urine, no. of visits in the year prior to randomization, no. of antihypertensives, use of renin angiotensin modulating drugs, use of diuretics,.
Model 4: Model 3 + center related: center size, academic status.
η^2= is a measure of effect size for use in ANOVA, B = unstandardized regression coefficient (representing difference in BP in mm Hg with center B), *p*= *p*-value in statistical analysis.

Figure 2: percentage of patients achieving BP goals in nine centers. Black bars represent the oscillometric BP goal, light grey bars represent the office guideline derived goals and dark grey bars represent a goal of 140/90 mm Hg.

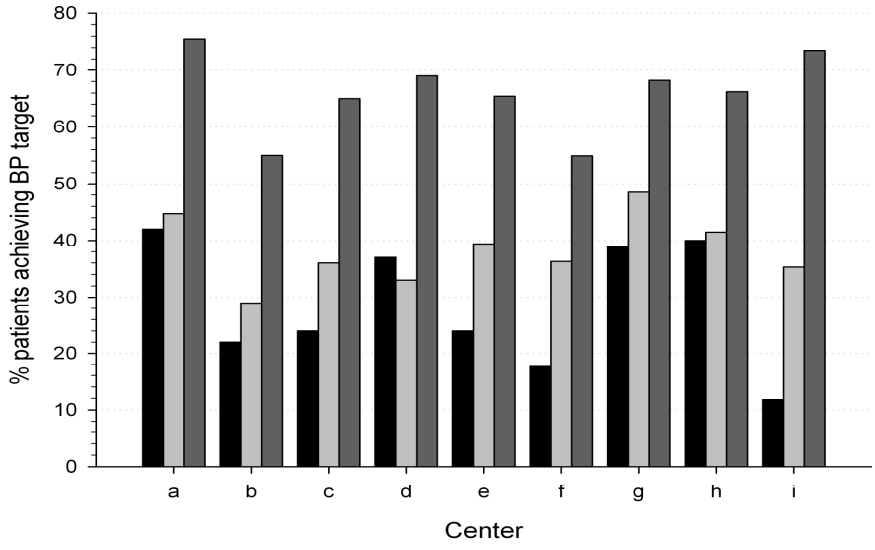

Figure 3: percentage of patients/center with diastolic BP < 70 mmHg per center. Black bars represent the patients not achieving the study treatment goal and the light grey bars represent patients who do meet the study goal.

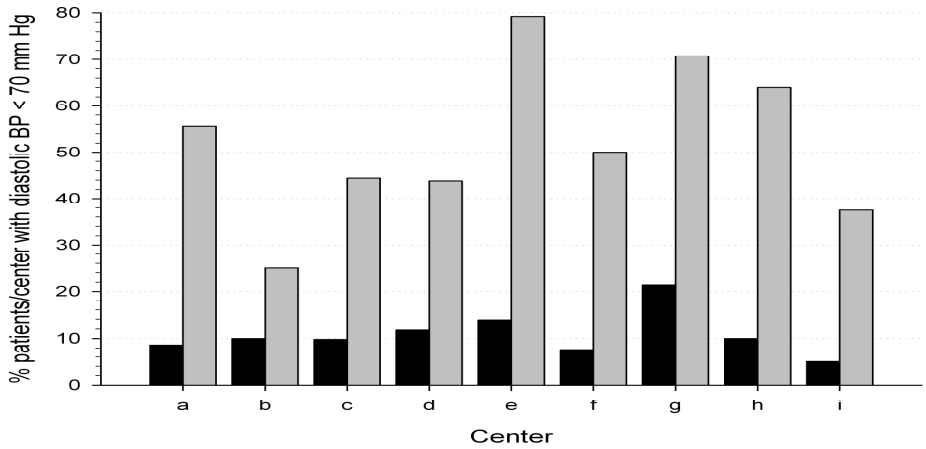

Figure 2 illustrates that differences between centers were present for all three treatment goals, although the smallest range was found when 140/90 mmHg as treatment goal is applied. In some centers a marked difference between achievement of the oscillometric BP goal and office BP goal could be appreciated (e.g. hospitals F and I). (Figure 2)

3. Could low diastolic BP be a factor obstructing achievement of treatment goals?

A diastolic BP <70 mm Hg was present in 170 (21.6%) patients. This is shown per hospital for patients who do and do not meet the study treatment goal. (Figure 3) In 62 of 587 patients not on target (10.6%) diastolic BP was below 70 mm Hg with no significant differences between hospitals.

Discussion

The present study shows that there are substantial and clinically relevant differences between centers with regard to achieved systolic and diastolic BP levels in CKD patients and percentages of patients achieving adequate BP control. These

differences persist after adjustment for various patient, kidney disease, treatment and hospital characteristics.

Adequate BP control in hypertensive patients is notoriously difficult and may show important differences between populations. Even more so in the CKD population because of the added disturbed sodium and water handling. Differences between countries may be attributed to the use of different guidelines, differences in lifestyle factors, healthcare organization and racial distribution.(21) In the present study, all patients were subject to the same set of guidelines, to the same healthcare organization and mostly of Caucasian race. It seems fair to conclude that these factors cannot explain the differences observed between hospitals. In addition, potential differences between patients in centers in several lifestyle factors were taken into account in our analysis.

In the present analysis, we went at length to take possible confounders into account.(22) Patient characteristics including socioeconomic status (Model 1) and characteristics of kidney disease (Model 2) did contribute and explained partially the differences between hospitals. Treatment and hospital related factors (Models 3 and 4) did not markedly change the observed associations. The fact that BP lowering therapy did not affect differences between centers may be explained by the high prevalence in all hospitals of the use of both diuretics and agents that interfere with RAS. So, Model 4 showed that despite adjusting for multiple factors, differences between hospitals persist. These results necessitate the consideration of yet additional factors, which may be of relevance.

Firstly, we addressed the question whether the technique/ device is the source of the difference. For that purpose, we also studied the last BP measured by the physician during the visit at the outpatient clinic prior to inclusion (a manual sphygmomanometric measurement using an aneroid device). Figure 1 showed that

these office BPs substantial differed between hospitals, indicating that the observed difference between hospitals was not explained by the different oscillometric devices. Moreover, BP differences existed between centers that use the same oscillometric device (e.g. center A and I both used the Datascope device, centers D, E, G an H all used the Critikon device).

It must be noted that in some centers a marked difference between oscillometric BP and office BP was present. This might indicate that the technique and situation of measurement affected results to a certain extent as stated recently by Becker and Wheeler, although all office-measurements were performed in the office by the internist using an aneroid sphygmomanometric device during the visit.(23) (Figure 2)

A second factor is that a yet unmeasured patient characteristics may have (partially) contributed to the center effect. These factors may include ethnicity, living environment and adherence to the prescribed treatment. Our cohort included patients from North-Africa, the Middle-East, Turkey and Northern Europe and all these different ethnicities were classified as Caucasian. The prevalence of these ethnicities is variable in the various regions of the Netherlands and may have been different between hospitals, which might have affected the results.(24;25) Non-adherence to therapy is a well known cause for not achieving BP goals and may be different between hospitals and possibly also affected by ethnicity.(26;27) Also environmental issues (i.e. crime, street noise, crowded housing) could affect BP and be distributed unevenly between the regions in which the hospitals are located.(25) However, these factors have not been specifically addressed in this study.

A third and most relevant factor in explaining the center differences may have been the attitude of the physician towards BP management. We have analyzed the data on the level of the hospital, not the physician. As such detailed data has not

been collected in the MASTERPLAN study, the present dataset does not allow such an analysis. The hospitals were however comparable with regard to the number of visits and the number or type of prescribed antihypertensives.

Although all physicians had access to and were familiar with the same set of guidelines, we unfortunately had no data on the target levels of BP that physicians in hospitals actually pursue.(28) Part of the observed differences could therefore be explained by different treatment goals: for example in one hospital the physicians might target BP's below 130 mmHg systolic, whereas in another hospital a systolic BP of 140 mmHg was considered adequate. Figure 2 showed that center differences appeared less obvious when applying a goal of 140/90 for the office BP measurement, possibly illustrating this phenomenon. Since the difference between hospitals was still statistically significant, this factor does not fully explain the hospital-effect.

The perceived importance of BP control could differ between physicians and hospitals and might possibly explain center-differences Physician inertia (i.e. the tendency not to adjust the intensity of treatment, despite the fact that a risk factor does not meet the treatment goal) has been identified as important factor affecting BP control and is also part of the physician attitude towards BP management.(29;30) However, as no information has been collected on these aspects, it was not addressed in this study.

A fourth aspect that could have affected treatment efficacy was the attainment of a low diastolic BP. Several studies have cautioned against lowering diastolic BP below 70 mm Hg, especially in patients with vascular disease. This trend may hamper treatment of patients with high pulse pressure, since adequate lowering of systolic BP in these patients will often cause diastolic BP below 70 mmHg. Our data did not allow for a definite conclusion on this issue.

Limitations

Our study has some limitations. The present analysis was performed on baseline data of CKD patients who have consented to participate in a randomised controlled trial. Therefore, the results might not be generalizable to the general CKD population. Further, all automated devices were validated within the centers, but were not all from the same manufacturer. We cannot exclude the possibility that this is of relevance.

Finally, at the start of the study, we did not expect to find this center effect. Therefore, we may not have collected sufficient data to evaluate this finding in much more depth, for instance daily defined dosages of antihypertensives could have illustrated some differences in treatment. Because of the numerous different antihypertensives applied in the cohort at baseline. Daily defined dosages could not be calculated. However, it seems reasonable to assume that this center effect is to be explained on the level of the physician.

In conclusion, the present data indicate that there are substantial and most likely clinically relevant differences between centers in the quality of BP control in CKD patients. Our analysis suggests that this may be explained by differences on the level of the physician. Further studies are necessary to address this possibility in more detail. It is attractive to hypothesize that this reveals additional opportunities to improve the quality of care.

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Chapter 3.

Self-efficacy and long term medication use in patients with chronic kidney disease.

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Self-efficacy and long term medication use in patients with chronic kidney disease.

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Abstract

Background

Long term medication use in patients with chronic kidney disease is necessary to prevent further kidney damage. Medication adherence is positively influenced by high self-efficacy ratings.

Aim

To determine if discussing self-efficacy scores, with regard to long term medication use by patients with chronic kidney disease, leads to higher self-efficacy scores.

Method

A total of 54 patients, randomized to a control and intervention group, rated their self-efficacy using the Long Term Medication Behaviour Self-Efficacy Scale (LTMBSES). Their scores were only discussed in the intervention group. Self-efficacy enhancing interventions were used to influence the self-efficacy scores.

Results

The intervention group had significant higher self-efficacy scores at posttest ($p= 0.013$).Transplantation had no effect on the mean self-efficacy. Patients ≤ 55 years had significant higher self-efficacy scores than patients > 55 years ($p=0.015$).

Conclusions

Discussing self-efficacy scores leads to increased self-efficacy scores in patients with chronic kidney disease.

Introduction

The number of patients with chronic kidney disease (CKD) is increasing and therefore also the need for renal replacement therapy. CKD is a condition that occurs when both kidneys fail to function normally. This can have many causes but is most often due to nephrosclerosis (damage to blood vessels in and around the kidney) and diabetic nephropathy (kidney damage due to diabetes mellitus). Furthermore, CKD is affected by aging, obesity and lack of exercise.(1) The number of Dutch people with a kidney disease is estimated at about 40,000. The number of patients receiving kidney replacement therapy (dialysis and transplantation) is approximately 12,700.(2)

Patients with CKD at initiation of dialysis often have cardiovascular damage. Therefore, at an early stage of kidney disease the focus should be on prevention of kidney impairment, metabolic complications and cardiovascular disease.(1) Medication is one of the pillars of the standard treatment approach in patients with CKD. Moreover, the prescribed medication must very often be taken for the rest of the patient's life. Current practice shows that prolonged drug use proves to be difficult for most people. In Western countries 50% of patients with a chronic illness stop taking his/her medication within one year.(3) This percentage corresponds to the Dutch situation. Furthermore, only 30% of chronically ill patients use the prescribed medication all year long.(3) Lack of medication adherence is the main reason for suboptimal effectiveness of drug therapy and may lead to medical and psychosocial complications of the disease and a decrease in quality of life, and also leads to increased indirect costs such as those caused by absenteeism and extra use of health care.(3)

Optimal outcomes for preserving kidney function and prevention of cardiovascular disease can be achieved only if patients are supported and

encouraged in self-managing their disease (e.g. by support aimed at developing successful coping strategies for their lifelong medication regimen).(4) Research has shown that knowledge and instruction alone is insufficient for effective self-management.(5)

Self-management is defined as follows. The patient is making conscious decisions regarding the conduct of the therapeutic regimen in such a way that the patient's chronic illness is embedded in his/her daily life.(6) Bandura stated that the ability to perform certain behaviors, including self-management, is mainly influenced by the belief that someone is actually able to execute that behavior.(7) This belief is referred to as self-efficacy. Patients with high self-efficacy for medication-related behaviors will be able to sustain the behavior longer.(8) For patients with low self-efficacy the opposite applies.(8) Promoting self-efficacy leads to improved self-management outcomes, increases life expectancy and reduces the use of health care resources.(9)

Because self-efficacy has the potential to change health status, motivation and adherence to prescribed regimens, interventions aimed at promoting self-efficacy are promising with regard to improving outcomes for chronic diseases.(10) One possible intervention is to promote self-efficacy, based on a baseline measurement of individual self-efficacy scores and discuss these scores with the patient as a basis for nursing interventions.(5)

The aim of this study is to measure and discuss self-efficacy in relation to long-term medication use in patients with chronic kidney disease, irrespective of transplant status. With proven effectiveness, such a standard instrument could be used as (part of) a nursing intervention for enhancing self-efficacy and thus self-management regarding the use of medication. This has led to the following

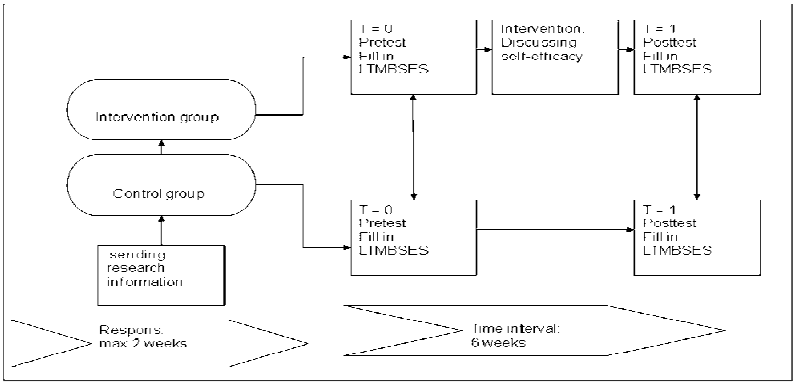
research question: What is the effect of discussing the self-efficacy regarding long-term medication use on the self-efficacy score in patients with chronic kidney disease?

Methods

Design

We chose a non-equivalent control group design with a pretest and a posttest. For this substudy we used the intervention and the control group of an ongoing clinical study, MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners). The MASTERPLAN study was carried out in nine Dutch hospitals over a period of 5 years from 2004 up till 2010.(11) MASTERPLAN aimed to prevent cardiovascular disease and kidney function deterioration. The MASTERPLAN patients in the intervention group received regular care from a nephrologist and additional counseling by a nurse practitioner. Patients in the control group received regular care of a nephrologist only. Between June and October 2007 the pretest, posttest and the intervention performed with the Long-Term Medication Behavior Self-Efficacy Scale (LTMBSES) took place.(Figure 1)

Figure 1: research design



Sample

The patients participating in the MASTERPLAN-study were included between April 2004 and September 2005. They were stratified for gender and kidney transplant status and then randomized to a control and an intervention group. At the time of data collection in our center, the MASTERPLAN population consisted of 84 patients, 45 in the intervention group and 39 in the control group. For this self-efficacy study patients in both groups were approached for participation. Additional inclusion criteria was the use of more than 5 different drugs.64 patients used ≥ 5 different drugs a day. Patients who met the selection criteria were sent study information and asked to use an application form to indicate whether they wanted to participate in the current substudy.

Data collection procedure

The pretest and posttest for both groups (or T=0 and T=1) took place within six weeks. The LTMBSES was sent to patients in the intervention group two weeks prior to the visit. Patients were instructed to respond within a week to assure adequate preparation for the investigator. Four weeks after the intervention the posttest was performed.

Patients in the control group received the LTMBSES. The second one following five weeks after reception of the first.

De Geest *et al*. and Denhaerynck *et al*. have developed and validated the LTMBSES to measure self-efficacy in relation to long-term medication use in (kidney) transplant patients.(8;12) The instrument, a Likert scale, consists of total 27 items about skills related to medication use, and has three substantive dimensions. Each dimension contains a number of mutually influencing sub-themes derived from the self-efficacy theory of Bandura: personal attributions (7 items), environmental factors (13 items), and task-related and behavioral factors (7 items) (see Table 1).

The self-efficacy score was computed by taking the mean of the scores (1 = "unlikely" to 5 = 'certainly') at each of the 27 items.(7) High scores (4 or 5) are an indication of a high self-efficacy and scores of 1 or 2 are an indication of low self-efficacy. The items are arranged in increasing skill difficulty.(13)
Cronbach's alpha of the original LTMBSES was 0.86 and criterion validity was established using Generalized Estimating Equations, which showed that the LTMBSES predicted medication adherence ($p < 0.0001$).(12;14)

Table 1: Dimensions, sub-themes and related items

Dimension	**Sub-theme**	**Item on questionnaire**
Personal attributions	Emotional distress	17,21
	Perceived health status	10,18,20,23
	Normal state	22
Environmental factors	Routine	1,6,7
	Distraction	13,16,19,24-27
	Medication expenses	3
	Social support	5,15
Task-related and behavioral factors	Medication aids	4
	Medication schedules	11,12
	Medication delivery system	2
	Side effects of medication	8,9,14

The intervention

All nurse practitioners had been trained in motivational interviewing as a tool to help improve self-management in this group of patients.
After informed consent was procured, patient's self-efficacy was scored using the Long-Term Medication Behavior Self-Efficacy Scale (LTMBSES). The results of this questionnaire were discussed using the motivational interviewing technique in patients randomized to the intervention group.
At the pretest in the intervention group items in which the patients scored lower than 5 were identified. Where patients felt uncertain about their ability to perform a skill successfully, the items were scored lowest. Discussing the self-efficacy scores

in the intervention group took place during a regular outpatient clinic visit to the nurse practitioner. Prior to the visit, the nurse practitioner had grouped the items for each dimension of the LTMBSES, stating what the score was. All items on which the patient scored less than 5 were presented to the patient. Together with the patient it was determined which items were discussed. If the patient had no preference, items with a score of 3 or 4 were discussed, because these scores give the best chance of increasing the self-efficacy. If the patient preferred to discuss items on which he scored a 1 or 2, those were discussed. This choice was interpreted as an indication that the patient was motivated to change behaviour in these items. A maximum of five items could be discussed at one outpatient visit due to the time available.

The method of discussion was structured (Table 2) but depended on what items were discussed by sub-theme. After identifying the problems or barriers that play a role in the lower (<5) scored items, the nurse and the patient tried to find possible solutions and on that basis concrete, achievable goals.

Table 2: Method of discussion

Dimension	**Approach**
Personal attributions	• Discuss with the patient how he/she dealt in the past with emotional circumstances. What worked and what did not. • Discuss what is needed even in physical complaints to continue to take medications, for example if there is gout.
Environmental factors	• Discuss if forgetting to take medication occurs under certain circumstances and explore if enlisting help from a family member.could be benifical. But taking medication can also be linked to certain activities. When financial contributions are a problem, seek alternative medication,
Task related and behavioral factors	• Discuss with the patient if schedules poses problems Medication schedules can be adjusted to the personal situation of the patient. Discuss if the patient experiences side effects. Alternative drugs can be tested or adjusted. • Timetables can be tried. • Discuss the knowledge about his/her medication

For example medication intake linked to a daily activity like brushing teeth. A number of self-efficacy enhancing interventions were used: such as using a medication box, keeping a diary (one week), to record experiences on successes and failures, providing positive feedback and encouragement for what was reached, and setting new goals when previous goals were achieved or adjust goals if they were not.(10)

Within this study, the LTMBSES was used as intervention and outcome: intervention of the LTMBSES was reflected in the discussion of the scores below 5 and the outcome of the LTMBSES was reflected in the difference between the post-test and the pretest, and was used as a measure of change.

Data analysis

All statistical analysis was performed with SPSS for Windows version 15.0. Baseline characteristics of intervention and control group were compared, and if age and whether or not being transplanted had an impact on the self-efficacy. Age can affect self-efficacy and possibly also being transplanted; research shows that precisely during this phase of life medication use can be a problem.(4;13;15) The independent t-test was used to test means in self-efficacy for both groups and itemized to being transplanted or not and age ≤ 55 years and> 55 years; the paired t-test was used to test means in self-efficacy on two intervals, T=0 and T=1 (before-after design) to compare within the intervention and control group, itemized to being transplanted or not and age ≤ 55 years and> 55 years. Significance level was set at P <0.05. For statistical purposes at least 30 patients in both groups were required.

Results

Baseline Characteristics

Ultimately 54 patients were willing to participate: 26 patients in the control group and 28 patients in the intervention group. The mean number of drugs was 7.65 per patient per day. The mean age was 59 years in the control group and 55 years in the intervention group. In both groups the number of men exceeds the number of women: 15 men in the intervention group and 18 men in the control group. The number of transplanted patients were almost identical for both groups: nine in the intervention group and 10 in the control group. These figures correspond with those of the MASTERPLAN study population.

Self-efficacy

The mean self-efficacy score at baseline was not significantly different for the intervention group and the control group (respectively 4.55 and 4.58). The intervention group scored lowest on items 3 and 23 (taking my medication when I need to pay extra for this and when I'm nauseous): 57% of patients scored a 4 or lower. The highest scores were on items 1 (taking medication when I'm at home) and 21 (take medication if I am sad): 93% of patients scored 5 on these items. The control group also scored the lowest on item 23: 65% scored 4 or lower. The control group scored highest on item 1: all patients scored 5. Items 1 and 3 belong to the subscale 'environmental factors' and items 21 and 23 to the subscale' personal attributions.

Table 3 shows a significant difference in the mean self-efficacy total score at posttest between control and intervention group ($p = 0.039$). For the self-efficacy scores on the subscales no significant differences were found between the control and intervention group. At the pre- and posttest in both groups there was only a

significant increase in mean self-efficacy total score ($p = 0.013$) in the intervention group. This difference is also significant for the subscales' environmental factors' and 'task-related and behavioral factors', $p = 0.024$ and 0.031 respectively.
With the patients in the intervention group items 20 and 23 (feeling sick and nauseous), 3 and 15 (pay extra and without anyone to help remember me) and 4 and 12 (without an aid and mealtime differs from medication time) were most discussed. These were the items the patients most wanted to talk about. The self-efficacy scores at posttest for items 20 and 23 were somewhat higher (respectively from 4.25 to 4.46 and 3.82 to 4.14) but not significantly different. At posttest still 32% of patients scored <5 for item 20 and item 23, in fact 53%. At posttest patients scored on items 4 and 12 significantly higher (respectively from 4.29 to 4.71, $p = 0.020$ and from 4.50 to 4.82, $p = 0.026$). Discussion of item 3 resulted in a significant increase in score from 4.07 to 4.56, $p = 0.002$. Item 15 at posttest showed a higher score, from 4.46 to 4.86, but this was not statistically significant ($p = 0.054$).

Self-efficacy influencing factors

Age had an impact on the mean self-efficacy score. Patients in the intervention group ≤ 55 years scored significantly higher after the intervention. For patients > 55 years there was no significant difference between the pre- and posttest. In the control group no significant difference was found in pre- and posttest analysis at any age level.
Gender and transplant status had no effect on the mean self-efficacy scores However, within the intervention group a difference in mean self-efficacy score was found between pre- and posttest in transplanted and non-transplanted patients. For transplant patients this difference was statistically significant ($p = 0.034$).

Table 3: Mean self-efficacy score at baseline and after six weeks for the Total LTMBSES and subscales personal attributions, environmental factors and task/behavioral factors in the intervention group and the control group [a], age and transplant status

Variables	N	Mean score at baseline (SD)	Mean score after six weeks (SD)	*P*-value †	*P*-value Mean diff. ‡
Total LTMBSES					0.039
Intervention group	28	4.55 (0.38)	4.70 (0.31)	0.013	
Control group	26	4.58 (0.43)	4.57 (0.43)	0.796	
Subscales					
Personal attributions					0.108
Intervention group	28	4.53 (0.50)	4.63 (0.42)	0.119	
Control group	26	4.57 (0.45)	4.53 (0.52)	0.505	
Environmental factors					0.107
Intervention group	28	4.55 (0.39)	4.71 (0.33)	0.024	
Control group	26	4.58 (0.53)	4.57 (0.50)	0.916	
Task/behavioral factors					0.097
Intervention group	28	4.52 (0.59)	4.74 (0.42)	0.031	
Control group	26	4.54 (0.57)	4.56 (0.54)	0.764	
Age					
Intervention group					
≤ 55 years	13	4.56 (0.35)	4.81 (0.21)	0.004	
> 55 years	15	4.54 (0.41)	4.60 (0.36)	0.498	
Control group					
≤ 55 years	14	4.54 (0.42)	4.56 (0.36)	0.782	
> 55 years	12	4.63 (0.47)	4.59 (0.52)	0.594	
Transplantation					
Intervention group					
Transplanted	10	4.62 (0.47)	4.76 (0.35)	0.034	
Not transplanted	18	4.51 (0.33)	4.66 (0.29)	0.083	
Control group					
Transplanted	9	4.59 (0.35)	4.63 (0.26)	0.618	
Not transplanted	17	4.58 (0.48)	4.54 (0.51)	0.525	

[a] Higher scale scores indicate higher self-efficacy scores.
† Paired T-Test. $P<0.05$ (2-tailed) for mean self-efficacy score at pretest and posttest within each group.
‡ Independent T-Test. $P<0.05$ (2-tailed) for mean difference at pretest and posttest between control and intervention group.

Discussion

This study shows that discussing the self-efficacy scores obtained with LTMBSES in patients with CKD receiving long-term ≥ 5 different medications a day, leads to an increase in self-efficacy. In this study, not therapy itself or the interventions that

increase self-efficacy where studied, but the added value of discussing the LTMBSES as an intervention was examined here. Which of these interventions is the most effective in increasing self-efficacy regarding drug-use, warrants further research.

However the LTMBSES, aside from being a validated tool to assess self-efficacy, also appears to be a useful /effective starting-point for interventions aimed at increasing self-efficacy with regard to medication use. A higher self-efficacy was achieved with items where an intervention took place with the exception of items 20 and 23 which belonged to the subscale 'personal attributions'. Many patients still scored <5 after discussing these items. This was also seen in the control group. Apparently, these items strongly influence the self-efficacy. In De Geest *et al*. patients indicate that health status (within subjects 'personal attributions') affects the accuracy of medication intake.(8) This was also what the patients in the intervention group indicated. Most frequently medication intake was postponed to a more suitable time.

Medication self-efficacy in patients ≤ 55 years is significantly higher than in patients > 55 years. This is consistent with findings of Sol *et al*.(15) Itemized to the intervention and control group, this difference also appears significant for the intervention group. It is possible that younger patients are more receptive to behavioral change than the older patients in the intervention group. More research on this subject is needed.

Within the intervention group there was a significant difference in mean self-efficacy score between transplanted and non-transplanted patients. Perhaps transplanted patients in the intervention group had a greater interest in an appropriate intake of specific medications to reduce the risk of rejection of kidney transplant.

The study has some (methodological) limitations. The relatively high self-efficacy scores in the intervention group could be explained by the participation of the patients in the MASTERPLAN study. Possibly this was a matter of a 'ceiling effect'. This Masterplan intervention group received specific attention and counseling by a nurse practitioner and this could result in a positive effect on self-efficacy In the control group the Hawthorne effect could play a role.

The small sample size precludes additional refinement of the analyses. Future studies with bigger sample size are needed. Because we used an existing intervention and control group and the intervention group was offered an additional intervention (discussing the LTMBSES), the conditions for both groups were at the start of the study not similar (non-equivalent). Therefore it is conceivable that other factors are responsible for the effect we found, although the average age, distribution of men and women and number of transplanted patients were comparable to the population of MASTERPLAN. No adjustment for any covariate was performed.

The LTMBSES has been developed for transplant patients. For this reason there are items that relate only to adverse events caused by specific (immunosuppressive) drugs (items 9 and 14). In this study only 35% of patients were transplanted.

It could also be that patients gave socially desirable answers. The patients were already coached for more than two years by the investigator, so a personal relationship had been established.

This study involved a minimal, one time, intervention. It is very likely that by discussing the self-efficacy scores several times in the long term, combined with feedback on achievement of goals, the self-efficacy will increase substantially..

Conclusion

The results of this study show that discussing self-efficacy scores regarding long-term medication use in CKD patients using the LTMBSES, results in increased self-efficacy. Because the groups differed at the beginning and end of the study and were already part of another ongoing clinical trial, other factors could have played a role and may have influenced the results.

Implications for practice

The results of this sub study of the MASTERPLAN-study could be a first step for other nurses to record self-efficacy regarding medication use in CKD patients. Various interventions can be used to increase self-efficacy. Because appropriate adherence to drug therapy is so difficult to maintain, increasing self-efficacy is likely to be an important contribution to effective self-management. Adjustments to the LTMBSES to better accommodate CKD patients are advisable.

In this study participants were already acquainted with the investigator who performed the intervention herself. In future research this situation needs to be avoided.

Additionally future studies should address the duration of the effect and the effects of multiple sequential sessions to address and improve self-efficacy.

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Chapter 4.

Results

Chapter 4.1

Nurse practioners improve quality of care in chronic kidney disease: two year results of a randomized study.

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Abstract

Background

Chronic kidney disease (CKD) is associated with increased cardiovascular risk. Here we evaluate whether strict implementation of guidelines aimed at multiple targets with the aid of nurse practitioners (NP) improves management in patients with CKD.

Methods

MASTERPLAN is a randomized controlled clinical trial, performed in nine Dutch hospitals. Patients with CKD (eGFR 20-70 ml/min/1.73m^2) were randomized to receive NP support (intervention group (IG)) or physician care (control group (CG)). Patients were followed for a median of 5 yrs. Presented data are an interim analysis on risk factor control at 2 yrs follow up.

Results

We included 788 patients (532 M, 256 F), (393 CG, 395 IG), mean (±sd) age 59 (±13) years, eGFR 38 (±15) ml/min/1.73m2, blood pressure (BP) 138 (±21)/ 80 (±11) mmHg.

At 2 yrs 698 patients (352 IG, 346 CG) could be analyzed. IG as compared to CG had lower systolic (133 vs. 135 mmHg; p= 0.04) and diastolic BP (77 vs. 80 mmHg; p=0.007), LDL cholesterol (2.30 vs. 2.45 mmol/l; p= 0.03), and increased use of ACE inhibitors, statins, aspirin and vitamin D. The intervention had no effect on smoking cessation, body weight, exercise or sodium excretion.

Conclusion

In both groups, risk factor management improved. However, changes in BP control, lipid management and medication use were more pronounced in IG than in CG. Lifestyle interventions were not effective. Coaching by NPs thus benefits everyday care of CKD-patients. Whether these changes translate in improvement in clinical endpoints remains to be established.

Introduction

Chronic kidney disease (CKD) is consistently related to excess cardiovascular morbidity and mortality. The benefits of blood pressure (BP) management on cardiovascular risk in CKD have not been shown in dedicated trials although several post-hoc subgroup analyses among CKD patients have suggested benefit.(1;2) Only recently statins were shown to be effective to reduce cardiovascular risk in CKD patients in the Study of Heart and Renal Protection.(3) Up till now intervention studies targeting other single risk factors to lower cardiovascular events (ADVANCE, CREATE, CHOIR) have not been very successful in CKD patients.(4-6)

Similarly, few strategies besides lowering of blood pressure and proteinuria have proven effective to attenuate the deterioration of renal function in patients with CKD.(7)

One of the possible explanations is that CKD is a multifactorial disease process in which both traditional cardiovascular risk factors and non-traditional risk factors (inflammation, CKD-metabolic bone disease, anaemia, proteinuria) interact. No single factor may play the major causative role. Based on this hypothesis it can be expected that a multifactorial approach is the most appropriate way to reduce

cardiovascular morbidity and preserve kidney function in patients with CKD. Such a strategy was proven effective in diabetic patients.(8)
Indeed, guidelines for the treatment of CKD involve management directed at multiple treatment targets. The guidelines published in 2003-2005 however were based upon extrapolation from other populations because of the paucity of data in patients with CKD.(9) Implementation of these guidelines in routine clinical practice is difficult. We, and others, have shown that treatment targets are often not met.(10-12) In addition, differences between centers were present.(13;14) Positive results from single-centre studies may therefore not be generalizable.
To address the need for improvement in CKD care we evaluated the added value of specifically trained nurses in the care of CKD patients. In similar study protocols, specialized nurses, cooperating in teams with doctors, have improved care in outpatients with diabetes, myocardial infarction and heart failure.(8;15-17) To evaluate this hypothesis the randomised controlled Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners (MASTERPLAN) study was designed. We present the interim results after two year of follow-up, on improvement in care, attainment of treatment targets, and between-center differences.

Materials and methods:

Design

The MASTERPLAN study [Trial registration ISRCTN registry: 73187232 (http://isrctn.org)] is a randomized controlled trial conducted in nine hospitals with a nephrology department in the Netherlands. The trial is reported in accordance with the CONSORT guidelines.(18)

Rationale and design have been published elsewhere.(19;20) The effects of a multitargeted treatment regimen executed by a specialized nurse under the supervision of, and in collaboration with, a nephrologist are compared with the care delivered by the patients own nephrologists. In both arms of the study, the same treatment guidelines apply. The primary end point is a composite of fatal and nonfatal myocardial infarction, stroke and cardiovascular mortality. Secondary end points are all-cause mortality, achievement of treatment goals for the various risk factors, decline of kidney function and quality of life.

Patients were eligible for inclusion when 18 years old and diagnosed with CKD with a creatinine clearance estimated by the Cockcroft-Gault equation between 20 and 70 ml/min. The following conditions were considered exclusion criteria:

- A renal transplant less than a year before inclusion
- Acute renal failure or rapidly progressive glomerulonephritis established by the treating physician
- Any malignancy less than five years before inclusion other than basocellular or squamous cell carcinoma of the skin.
- Participation in other clinical trials requiring the use of study medication

Recruitment began in April 2004 and continued until December 2005. From April 15th 2005 until the end of the inclusion period the Cockcroft-Gault equation was modified to take into account body surface area according to then prevailing insights into the applicability of formulas to estimate renal function.(21-24) This modification was approved by the medical ethics committee.

After the baseline evaluation, the patients were randomized to either nurse practitioner (NP) care or usual care in a 1:1 ratio. Randomization to treatment was stratified by center, gender and renal transplant status using a web-based randomization module and performed in predefined blocks. Patient, NP and physician were familiar with the treatment allocation. All investigators handling

the data however were blinded until june 2010. Follow-up continued until June 2010. Endpoint evaluation and data-analysis is scheduled for 2011. The study was approved by an institutional medical ethics committee and all subjects gave informed consent. All participating hospitals are teaching hospitals that offer a full range of nephrology treatment including kidney replacement therapy (both hemodialysis and peritoneal dialysis) and are involved in the care of kidney transplant recipients. Three hospitals are university clinics that offer tertiary care and have kidney transplant programs. The number of beds per hospital ranges from 414 to 953.

To all patients the same set of guidelines and treatment goals, represented in Table 1 and Table 2, apply. Both patients and physicians were provided with information about the beneficial effects of multifactorial risk factor management regardless of treatment allocation. In the intervention group NPs, supervised by a qualified nephrologist, actively pursued lifestyle intervention (physical activity, nutritional counseling, weight reduction and smoking cessation), the use of specified cardioprotective medication and the implementation of current guidelines. The NP checked regularly whether treatment goals were met and when deemed appropriate adjusted treatment to achieve target values.

Modification of therapy was executed according to flowcharts that were derived from then current guidelines. For lifestyle-modifiable risk factors the NP applied motivational interviewing as a technique to improve lifestyle in the intervention group.(11)

Additionally patients were seen by a specialist regularly (although no minimum frequency was required in the study protocol). Acetylsalicylic acid was included in the intervention because of the then proposed status of CKD as a coronary heart disease risk equivalent and the possible (but untested) benefits of acetylsalicylic acid in this context.(25;26) This was in line with a then valid guideline firmly

advocating the use of aspirin in primary prevention in patients with diabetes mellitus (which was downgraded however in a later version).(27;28) Use of aspirin was deemed contraindicated by protocol if patients had: a history of a cerebral hemorrhagic event, autosomal dominant polycystic disease with a family history of cerebral hemorrhagic events, a known bleeding tendency or a history of pyrosis, reflux or gastrointestinal bleeding.

Physician care comprised of 'usual care' conform the guidelines mentioned in table 1 and 2. In contrast to the intervention group and in agreement with real life practice no extra incentives to adhere to the guidelines were supplied.

Patients in the intervention group visited the NP at least every three months, whereas the frequency of visits of the control patients was left to the discretion of his/her nephrologist. Medication use was recorded every three months in an online case report form as were office BP, bodyweight and predefined laboratory results. In both patient groups twice yearly standardized oscillometric BP measurements after 15 minutes of supine rest were taken.

Annually ankle brachial index and evaluation of end points was performed in both intervention and control groups. Additionally patients filled out questionnaires regarding quality of life and physical activity on a yearly basis.

Under the assumption that patients were in steady state, sodium excretion was applied as a measure of sodium-intake. Blood was drawn and a 24 hour urine sample was collected. Blood and urine samples were analyzed locally. Medical history was obtained from the medical records. History of CV disease was defined as a history of myocardial infarction, stroke or vascular intervention. Diabetes mellitus (DM) at baseline was defined as the use of glucose lowering drugs or a fasting glucose 7.0 mmol/l. Adherence to the Dutch Guidelines of Healthy Physical exercise was determined with the validated SQUASH questionnaire.(29)

Table 1: Goals and relevant guidelines for cardiovascular risk factors in MASTERPLAN

Risk factors	**Goal**	
Blood pressure	</= 130/85 mm Hg[a]	
Proteinuria		
Protein excretion in urine	< 0.5 g/day	
Lipids		
Fasting LDL[b]	< 2.6 mmol/l	
Anemia		
Hemoglobin concentration	> 6.8 mmol/l AND </= 7.4 mmol/l[c]	
Glucose		
Fasting glucose	< 7.0 mmol/l	
Non Fasting glucose	< 9.0 mmol/l	
Calcium/Phosphate metabolism		
Phosphate	</= 1.5 mmol/l	
PTH[d]	eGFR[e] > 30ml/min	< 7.7 pmol/l
	15-30 ml/min	7.7-12.1 pmol/l
	<15 ml/min	16.5-33 pmol/l
Healthy Nutrition		
Protein	0.8 –1.0 g /kg ideal bodyweight/ day	
Sodium excretion	100 mmol/24 hr	
Fat	Reduce fat, unsaturated fats preferred	
Energy	30-35 kcal/ kg ideal bodyweight/ day	
Overweight		
Body mass Index	<25 kg/m^2	
Physical activity	5x/week 30 minutes moderate activity	
Smoking	To Quit	

A: In case of proteinuria > 1g/day: 125/75 mm Hg;B: LDL = Low density lipoprotein; C: In case of erythropoiesis stimulating agent; D: PTH = parathyroid hormone; use; E: eGFR= estimated Glomerular Filtration Rate

Table 2: Standard medication to reduce cardiovascular risk in MASTERPLAN

Medication	**Recommended dose**	**Point of impact**
Statin	e.g. atorvastatin 10 mg daily (or comparable dose of other statin)	Lipid-metabolism
Acetylsalicylic acid	80 mg daily	Thrombocyte aggregation
ACE inhibitor or Angiotensin Receptor Blocker	e.g. enalapril 5 mg twice daily (or comparable dose of other ACE inhibitor) or irbesartan 75-150 mg (or comparable dose of other ARB) daily	Blood pressure, renal function and cardiac pre- and afterload
Active vitamin D	e.g. alfacalcidol 0.25 μg daily if eGFR* is below 50 ml/min/1.73m^2	Bone-metabolism

*: eGFR= estimated Glomerular Filtration Rate

The underlying diagnosis of kidney disease was determined by the treating physician and categorized using the ERA-EDTA (European Renal Association) registration criteria. To allow for comparisons with other studies, we report eGFR using the abbreviated MDRD formula.(30)

Statistical analysis

Baseline characteristics have been expressed as means (SD) or proportions. For non-parametric data medians [range] have been supplied.

To address the effect of the intervention on risk factors after two year of follow-up we used generalized estimating equations (GEE) to assess time-dependent mean changes in risk factors within and between treatment arms.

The main assumption of the GEE approach is that measurements are assumed to be dependent within subjects and independent between subjects. The correlation matrix that represented the within-subject dependencies was estimated using an autoregressive relationship (i.e., correlation between variables within subjects are assumed to decline with time between the measurements). For the current analysis, the interest was in the mean difference over time in risk factor levels between treatment arms. GEE analyses were performed using the on trial measurements with adjustments for baseline measurements. All *p*-values were two-sided, and *p*-values less than 0.05 were considered to indicate statistical significance. No adjustment for multiple statistical testing was made.(31)

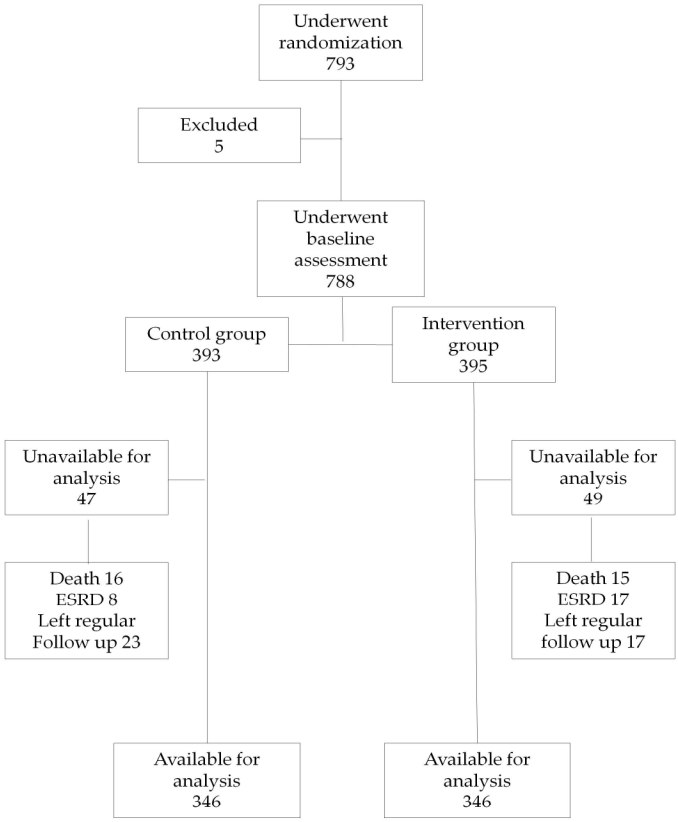
We also evaluated if the specialized nursing care reduced the differences in care between centers. To this end we calculated the absolute difference between the group mean and center mean for each risk factor. Relation of the absolute differences between group means and center means with time was then calculated using a Spearman correlation coefficient, with a negative correlation illustrating a

reduction of between-center differences over time. All analyses were performed with SPSS 17.0 (SPSS inc., Chicago, USA).

Results

About 60% of patients deemed eligible by their physician and asked to participate in the study, actually participated and was included. The main reasons for non-participation were: reluctance of the patient to changes in drug therapy and inability of the patient to attend the required visits.

Figure 1. Enrolment, randomization, and follow-up of study participants.



793 patients were included in the study. Three patients did not meet inclusion criteria and two declined participation after randomization. At two years of follow-up 346 in the control group and 346 patients in the intervention group were available for analysis (figure 1). Baseline demographics are shown in Table 3. The mean age of patients was 59 (±13) years. 6.7% of patients is KDOQI CKD class 1 or 2, 60.8% class 3, 30.2% class 4 and 2.4% class 5. 17% of patients had no albuminuria, 49 % had microalbuminuria and 34% had overt proteinuria.
All characteristics were well balanced between the groups apart from a history of cardiovascular disease which was more prevalent in the intervention group and current smoking which was less prevalent in the intervention group.

The changes in risk factors after one and two years are shown in Table 4. Both in the intervention and control group changes in several risk factors were found. In both groups systolic BP, diastolic BP, LDL-cholesterol, haemoglobin and percentage of smokers decreased. In both groups statistically significant reductions in eGFR and an increase in use of ACE-inhibitors or Angiotensin receptor blockers, statins, vitamin D and aspirin were found. (Table 4)

Systolic BP, diastolic BP and LDL-cholesterol were lower in the intervention-group at two years and also declined significantly more than in the control-group. At two years the difference between the two groups was 2 mm Hg for systolic, 3 mm Hg for diastolic BP and 0.15 mmol/l for LDL-cholesterol.
Use of cardio protective medication increased more after two years in the intervention group than in the control group: ACE-inhibitors or Angiotensin receptor blockers (+8.6% vs. +3.7%), statins (+21.2% vs. 14.2%), acetylsalicylic acid (+23.4% vs. +9.4%) and vitamin D supplements (+28.4% vs. 16.1%).

20.4% of patients in the intervention group used coumarin derivatives and an additional 4.3% had a contraindication and were therefore not prescribed acetylsalicylic acid.
In contrast, there were no significant changes in lifestyle variables between the groups. At two years 46% of patients achieved the BP goal in the intervention group whereas this was only 35% in the control group (p=0.003). For the LDL goal this was 69% and 60% respectively (p=0.02).

Table 4 and figure 2 illustrate that the effect of most interventions was most prominent in the first year of the study. Changes were maintained during the second year. This applies both for the intervention and the control group.
We previously showed that differences in quality of care and BP between centers could be partially attributed to physician related factors.(13) Therefore we hypothesized that the execution of patient care by uniformly trained NPs would attenuate between-center differences. This was analyzed by comparing the center means for the variables influenced by the intervention (systolic BP and LDL-cholesterol) to the cohort mean at baseline, one year and two years.
For both risk factors the variation between the centers decreased with time in the intervention group as illustrated in Figure 3.

Discussion

Our study showed that added support by highly qualified NPs improved the quality of treatment of patients with CKD. Specifically, we observed lower blood pressures, lower LDL cholesterol, and increased use of aspirin, vitamin D, ACE-inhibitors in the intervention group. However, in contrast with our expectations, the NP guided intervention did not result in major changes in lifestyle factors.

Table 3: Baseline characteristics

Parameter	**Control group (n=393)**	**Intervention group (n=395)**
Age (yrs)	59.3 (12.8)	58.9 (13.1)
Gender (male) (%)	68	67
Race (Caucasian)	93	91
Nephrological diagnosis (%)		
Diabetic nephropathy	9	11
Renovascular	28	26
Glomerulonephritis/ interstitial nephritis	34	28
Congenital disease	13	11
Unknown	16	24
Kidney transplantation (%)	14	14
Prior cardiovascular disease by questionnaire (%)	25	33
Creatinine (mcmol/l)	181 (67)	182 (64)
eGFR (ml/min/1.73m^2)	37.7 (14.0)	38.4 (15.2)
Office Systolic BP (mm Hg)	139 (22)	138 (20)
Office Diastolic BP (mm Hg)	81 (11)	80 (11)
Proteinuria (g/24 hr) Median [25/75th percentile]	0.3 [0.1-0.8]	0.2 [0.1-0.8]
Albumin creatinine ratio (mg/mmol) Median [25/75th percentile]	18.8 [6.8-51.9]	15.0 [5.6-47.5]
LDL-cholesterol (mmol/l)	2.74 (0.90)	2.78 (0.95)
Haemoglobin (mmol/l)	8.2 (1.0)	8.2 (1.0)
History of DM (%)[a]	23	26
Phosphate (mmol/l)	1.10 (0.24)	1.10 (0.25)
PTH (pmol/l) [median 25th/75th percentile]	9 [5-14]	9 [5-15]
Sodium-excretion (mmol/24 hr) [median 25th/75th percentile]	150 [113-189]	148 [116-195]
BMI (kg/m^2)	27.2 (4.9)	27.0 (4.6)
Physical exercise (adherence to Dutch physical activity guideline) (%)	60	57
Physical activity (activity score=intensity/min/week/1000)	6182 (4467)	5803 (3891)
Smoking (%)	24	19

Values are proportions, means with corresponding standard deviation, or median with inter quartile ranges, whenever appropriate.
a: History of diabetes mellitus defined as using blood glucose lowering medication or fasting glucose >7.0 mmol/l.

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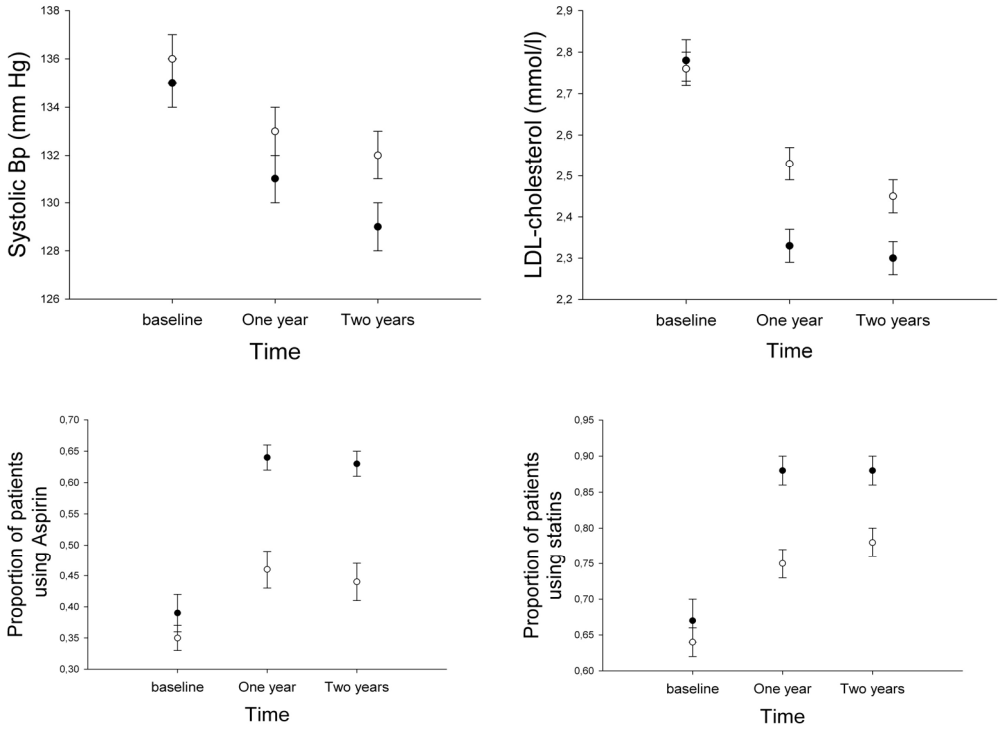
Table 4: Effects of the intervention after one and two years

Parameter	Baseline		Year 1		Year 2		*p*-value for differences between treatment group
	Control	Intervention	Control	Intervention	Control	Intervention	
N	N=393	N=395	N=373	N=374	N=346	N=352	
eGFR (ml/min/1.73m²)	37.7 (14.0)	38.4 (15.2)	35.8 (15.2)	36.7 (15.6)	35.0 (16.2)*	36.2 (16.4)*	0.36
Office Systolic BP (mm Hg)	139 (22)	138 (20)	137 (20)	133 (20)	135 (19)*	133 (21)*	0.04
Office Diastolic BP (mm Hg)	81 (11)	80 (11)	80 (11)	78 (11)	80 (11)*	77 (10)*	0.007
Proteinuria (g/24 hr)	0.3 [0.1-0.8]	0.2 [0.1-0.8]	0.3 [0.1-1.0]	0.2 [0.1-0.8]	0.3 [0.1-1.0]	0.2 [0.1-0.7]	0.33
Albumin Creatinine ratio (mg/mmol)	18.8 [6.8-51.9]	15.0 [5.6-47.5]	17.7 [6.6-53.1]	13.4 [4.7-41.1]	19.1 [7.0-62.4]	12.3 [5.0-46.3]	0.56
LDL-cholesterol (mmol/l)	2.74 (0.90)	2.78 (0.95)	2.53 (0.89)	2.33 (0.74)	2.45 (0.81)*	2.30 (0.75)*	0.03
Haemoglobin (mmol/l)	8.2 (1.0)	8.2 (1.0)	8.1 (1.0)	8.1 (1.0)	8.0 (1.1)*	8.1 (1.1)	0.85
HbA1C (%)	6.1 (0.9)	6.1 (0.9)	6.1 (0.9)	6.1 (0.8)	6.1 (0.9)	6.1 (0.8)	0.95
Phosphate (mmol/l)	1.1 (0.2)	1.1 (0.2)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	0.70
Calcium (mmol/l)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	0.43
PTH (pmol/l)	9 [5-14]	9 [5-15]	8 [5-14]	8 [5-14]	9 [6-15]	9 [5-15]	0.64
Sodium excretion (mmol/24 hr)	150 [113-189]	148 [116-195]	152 [120-191]	149 [116-198]	150 [117-190]	150 [120-193]	0.95
BMI (kg/m²)	27.2 (4.9)	27.0 (4.6)	27.1 (4.9)	26.8 (4.6)	27.0 (4.7)	26.8 (4.7)	0.53
Physical exercise (activity score=intensity/min/week/1000)	5220 [3180-8520]	5175 [2885-7930]	4740 [2689-7380]	4800 [2100-7740]	5340 [2465-7793]	4920 [2330-7628]	0.31
Smoking (%)	24	19	22	16	17*	14	0.06
Use of ACE or ARB (%)	77.6	81.1	84.0	91.6	81.3*	89.7*	0.003
Use of statin (%)	63.4	66.9	74.8	87.7	77.6*	88.1*	<0.001
Use of acetyl salicylic acid (%)	34.6	39.4	46.2	63.4	44.0*	62.8*	<0.001
Use of vitamin D (%)	23.9	22.0	32.8	40.9	40.0*	50.4*	0.05
Use of phosphate binder (%)	13.2	9.6	15.2	11.0	18.4*	15.3	0.11

eGFR = estimated glomerular filtration rate, BP = blood pressure, BMI = body mass index, ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, * = *p*-value for change over time within treatment group <0.05, results are mean (± sd) or median [25th-75th percentile].

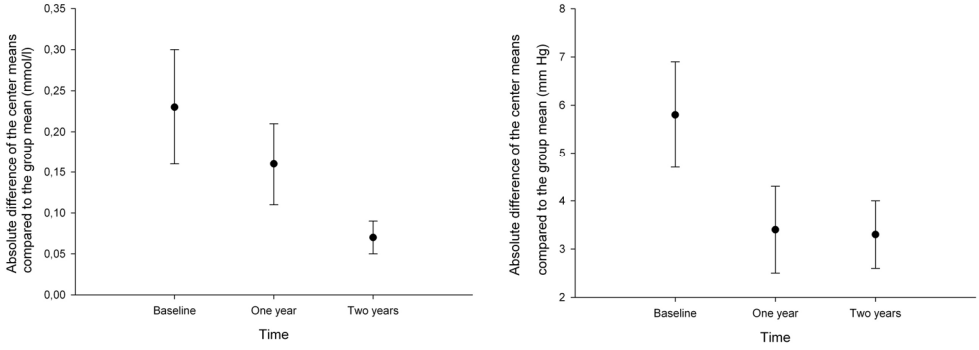
Figure 2: Changes in the first two years of the study
2a: Systolic BP: ●= Intervention group (*p*-value for change within group <0.001); ○= control group (*p*-value for change within group 0.004); *p*-value for change between groups 0.04
2b: LDL-cholesterol: ●= Intervention group (*p*-value for change within group <0.001); ○= control group (*p*-value for change within group <0.001); *p*-value for change between groups 0.03
2c: Statin-use: ●= Intervention group (*p*-value for change within group <0.001); ○= control group (*p*-value for change within group <0.001); *p*-value for change between groups <0.001
2d: Aspirin use: ●= Intervention group (*p*-value for change within group <0.001); ○= control group (*p*-value for change within group 0.008); *p-v*alue for change between groups <0.001.



Many studies have evaluated the effect of NP support in attaining treatment targets. Most studies were conducted in patients with diabetes(8;32-35) or patients with a high cardiovascular risk score.(36-40) They showed improvement in the management of some risk factors compared to usual care.

Figure 3: Center differences in the intervention group

3a: LDL-cholesterol: ●= Intervention group (*p*-value for change within group 0.003)
3b: Systolic BP: ●= Intervention group (*p*-value for change within group 0.04)



In general, pharmacotherapy modifiable risk factors such as BP and cholesterol improved in the intervention groups, although in many studies beneficial effects were limited to only one of the evaluated interventions.(8;33;35;37;40;41)
The size of the improvements of risk factors between baseline and two years in the intervention group particularly with regard to BP and LDL might well represent relevant improvements in cardiovascular risk.(42;43) However whether the smaller difference between intervention and control group in this study translates in improved cardiovascular risk after longer follow up still remains to be established. Some argue that multiple moderate improvements in several areas of risk factor management may translate in larger benefits on hard endpoints as was also shown in the study by Gaede et al.(8;44;45)
It is unclear whether even lower blood pressure goals would have resulted in lower BP in the intervention group.

A recent study in 500 Canadian patients with stage 3-4 CKD followed for two years compared family physician care with care by a specialized nurse under supervision of a nephrologist. They failed to observe beneficial changes in BP and lipid profile and also did not note any difference on cardiovascular endpoints.(46) The patients in this cohort were older, had better kidney function (higher eGFR and lower proteinuria) and had at baseline better controlled systolic BP (on average 8 mmHg lower). These differences can certainly explain the different results between CanPREVENT and MASTERPLAN.We hypothesized that specialized nursing care could also be of particular benefit by helping the patient in improving lifestyle. In our current analysis no such effect was observed. This was also reported by Gaede et al. They studied patients with diabetes mellitus II and observed improvement in BP, cholesterol, glycemic control and aspirin use. In contrast, lifestyle factors were not affected.(8;47) Earlier NP led intervention studies did show benefit in modifying the lifestyle factors studied in our study (smoking cessation, weight loss , dietary sodium restriction and physical activity) in single intervention studies.(48-53) In contrast, many recent reports in preventive medicine have pointed out the difficulties in reaching any relevant benefits in studies investigating a multiple health behavioural change. Effects were, if any, mostly limited in size.(39;54;55) A recent review by Blokstra et al. in patients with established cardiovascular disease, concluded that a multifactorial lifestyle intervention can affect diet, activity, smoking behaviour and reduce the occurrence of cardiovascular disease and/ or mortality particularly in high risk groups.(56) The original studies described had a far more rigorous lifestyle intervention than was applied in our study.(57) In other high risk categories the results were far less outspoken possibly suggesting that patients who had experienced a cardiovascular event were more motivated to execute lifestyle changes.(56)

Why then are no lifestyle benefits found in our cohort? Firstly CKD is a silent disease, and all efforts are taken as preventive measures. It is likely that CKD patients have lower motivation to ameliorate lifestyle than patients who have experienced a cardiovascular event. Secondly Jacobs et al. suggested that in a multifactorial intervention the number of possible choices may overwhelm the participants and thus result in lower effects.(58) This might also be relevant in our study, since we have formulated 11 treatment targets for our patients, four of which are to be considered lifestyle interventions.

Finally another effect might be relevant not alone with regard to lifestyle but also with regard to other risk factors. Because of the study-design patients were randomized within a center; therefore the same physician coaching the NP would see patients of the control-group during their outpatient visits. Patients in the control group might thus also experience better care than they would have gotten, had they been treated in a center not associated with the study. A possible indication of this is the clear reduction in the percentage of smokers in both cohorts. This effect is further illustrated in the control group by the reduction of LDL-cholesterol and the rapid increase in the prescription of statins and aspirin during the first year of the study. (Figure 2) The increase in treatment of cardiovascular risk factors in the control group could also be explained in another fashion, namely as a consequence of an increased nationwide awareness of cardiovascular risk in this period. Several key publications and guidelines were published prior to or during the early years of our study and may have prompted physicians to alter their therapeutic strategy. (e.g. KDOQi and Dutch federation of Nephrology guidelines).(59;60)

Earlier we reported clear between-center differences for several risk factors and explored this phenomenon more thoroughly for blood pressure.(13;14) We

suggested that physician related factors might explain part of the differences. Our current data support this view, since between-center differences were less for those risk factors that were improved in the nursing intervention group.
We conclude that specialized nursing care can help to improve specialist nephrological care to patients with stage 3 and 4 CKD. This is readily apparent with pharmacotherapy modifiable risk factors, but less so with lifestyle interventions. Whether this translates in improved cardiovascular risk remains to be established during the remainder follow-up of the study.

Limitations of the analysis

Not all interventions applied in our study can be considered evidence based or part of then current guidelines. Patients with an eGFR below 50 ml/min/1.73 m2 were supposed to receive active Vitamin D and certainly more current guidelines suggest measurement of vitamin D before supplementation.(61) Also aspirin was advocated in our study based upon the conviction of the study group that this might be beneficial in CKD, just like other groups had suggested.(25;26;62)
Another limitation is the earlier mentioned evident improvement of risk factor management in the control group. The effect of improved care in the control group could be an explanation for the modest differences between intervention and control and might also influence the effect on cardiovascular events.

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Chapter 4.2

Effect of a multifactorial intervention with the aid of nurse practitioners on cardiovascular outcome in patients with chronic kidney disease: results of a randomized controlled trial (MASTERPLAN).

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* contributed equally

Submitted

Abstract

Background

Strict implementation of current guidelines directed at multiple treatment targets with the help of nurse practitioners reduces vascular risk in diabetic patients. Whether this may also apply for chronic kidney disease (CKD) patients, is uncertain.

Methods

We randomized 788 patients with mild to moderate CKD (estimated GFR 20-70 ml/min) to receive additional intensive nurse practitioner support (intervention group) or standard nephrologist care (control group). The primary endpoint was a composite of myocardial infarction, ischemic stroke or cardiovascular death.

Results

During a mean follow-up of 4.62 years (range 0.05 to 6.08), mean blood pressure was significantly lower in the intervention group (132/77 mmHg) than in the control group (135/79 mmHg). Significant differences were found for LDL cholesterol (-0.11 mmol/l), triglycerides (-0.15 mmol/l), hemoglobin (+0.01 mmol/l), anemia (-2%), proteinuria (-0.12 gr/24h) and use of active vitamin D (or analogs) (+4.6%), platelet aggregation (+10%) and statins (+4.7%). No differences were found for smoking cessation, body weight reduction, sodium intake, physical activity or glycaemic control. Intensive control did not reduce the rate of the composite endpoint (21.3/1000 person-years in the intervention group versus 23.8/1000 person-years in the control group; hazard ratio 0.90 [95% CI 0.58, 1.39], $p = 0.62$). No differences were found in secondary event outcomes, including end stage renal disease (28.6 versus 34.4/1000 person-years; HR 0.83 [95% CI 0.57, 1.20], p=0.32)

Conclusion

A strategy of added intensified support by nursepractitioner care in CKD patients improved some risk factor levels, but did not significantly reduce the rate of myocardial infarction, ischemic stroke and cardiovascular death. (Trial registration ISRCTN registry: 73187232)

Introduction

Chronic kidney disease (CKD) is a known risk factor for cardiovascular disease (CVD).(1;2) This has been demonstrated for patients on kidney replacement therapy and patients with mild kidney dysfunction.(3) This increased CVD risk is attributed to traditional risk factors (e.g. hypertension, dyslipidemia, diabetes, male gender, smoking) and kidney disease specific risk factors such as anemia, albuminuria and calcium-phosphate disbalance.(4) The contribution of one risk factor to the CVD risk is small, but the combination of all factors results in a very high CVD risk.(4;5) Despite the existence of several guidelines, studies in hypertensive and dyslipidemic patients and other high-risk groups have demonstrated that goals for treatment are often not met.(6-11) The same holds for CKD patients.(12) Physicians usually do not have the time to address all relevant issues regarding CVD risk. Nurse practitioners may be of help. The benefits of coaching by nurse practitioners are evident in other high-risk populations.(13-15) Studies in patients with diabetes mellitus or heart failure showed that a multifactorial intervention implemented by nurse practitioners significantly improved metabolic control and reduced CVD.(13-15) Given the high CVD risk and the multitude of modifiable risk factors a multifactorial approach could also be of benefit for patients with CKD.(4;5). The aim of our study was to assess whether

the addition of nurse practitioner care to usual care by a nephrologist in patients with moderate to severe CKD aimed at strict implementation of current guidelines with emphasis on CVD medication and lifestyle changes, improves CVD outcome.(16)

Design and methods

Study design

MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) is a multicenter randomized controlled trial. Results are reported according to CONSORT guidelines.(17) The research protocol was approved by the local ethical committees and all participants gave written informed consent. Rationale and design have been published elsewhere.(16;18) In brief, subjects were recruited from the outpatient nephrology clinics of nine Dutch hospitals that offered a full range of nephrology treatment including kidney replacement therapy. Patients were eligible for inclusion when diagnosed with moderate to severe CKD (estimated glomerular filtration rate by the Cockcroft-Gault equation between 20 and 70 ml/min).

Recruitment began in April 2004 and continued until December 2005.

Randomization to treatment was performed in a 1:1 ratio stratified by center and kidney transplant status using a web-based block randomization module. All patients were subject to identical guidelines and treatment goals, which were described earlier.(16) At baseline information on medical history, physical activity and medication use was obtained by questionnaire. Patients underwent a physical examination and urine and blood samples were taken. These measurements were repeated annually. All laboratory measurements were performed in local laboratories.

In patients with overt proteinuria protein in urine was assessed in g/24 hr. However by design in patients with known microalbuminuria albumin in urine was measured in mg/24 hr and protein in g/24hr was not measured. To obtain one value for proteinuria in all patients, albumin values were converted to proteinuria value using the same approach as applied by KDIGO in their recent publications (i.e. multiplying albumin values by 3/2).(19)

Additionally both groups received an automated oscillometric blood pressure (BP) measurement every six months.

In the intervention group, a nurse practitioner, supervised by a qualified nephrologist, actively pursued lifestyle intervention (physical activity, nutritional counseling, weight reduction and smoking cessation), the use of specified mandatory medication (a statin, either ACE-inhibition or Angiotensin receptor blockade, active vitamin D (alfacalcidol) and aspirin) and the implementation of current guidelines.(Table 1) Modification of therapy was executed to achieve target values. The approach and coaching by nurse practitioners has been described earlier.(20) In their contacts with patients nurse practitioners aimed at pursuing strict adherence to guidelines and modifying lifestyle by improving self-management by the patient.

Endpoints

Primary outcome was a composite of myocardial infarction, ischemic stroke and CVD mortality. Myocardial infarction was defined as evident new ischemic changes on an ECG or an established rise and fall pattern of cardiac enzymes. Ischemic stroke was defined as characteristic clinical symptoms and evidence of recent cerebral ischemia using an appropriate imaging technique (CT-scan or MRI). CVD mortality was defined as death due to myocardial infarction, ischemic stroke, ruptured abdominal aneurysm, terminal heart failure or sudden death. An

independent endpoint adjudication committee, blinded for group assignment, reviewed source documentation for all suspected primary endpoints and deaths. Secondary endpoints were vascular interventions, all cause mortality and start of kidney replacement therapy.

Table 1. Risk factors that should be intensively addressed by the nurse practitioner in the MASTERPLAN study.

Risk factors	**Goal**	
Blood pressure	</= 130/85 mm Hg[a]	
Urinary protein excretion	< 0.5 g/24 hr	
Fasting LDL-cholesterol	< 2.6 mmol/l	
Hemoglobin concentration	> 6.8 mmol/l AND </= 7.4 mmol/l[b]	
HbA1C	< 7.0% (53 mmol/mol)	
Phosphorus	</= 1.5 mmol/l	
PTH	eGFR > 30ml/min	< 7.7 pmol/l
	15-30 ml/min	7.7-12.1 pmol/l
	<15 ml/min	16.5-33 pmol/l
Urinary sodium excretion	100 mmol/24 hr	
Body mass Index	<25 kg/m^2	
Physical exercise	5x/week 30 minutes moderate exercise	
Smoking	Quit	

Abbreviations: LDL= Low density lipoprotein, PTH = parathyroid hormone
a) In case of proteinuria >1.0 gr/24hr: 125/75 mm Hg
b) In case of erythropoiesis stimulating agent use

Statistical analysis

MASTERPLAN was originally designed to have a statistical power of 80% to detect a relative risk reduction of 50% or more for intensive care compared with usual care, based on a two-tailed test with an alpha level of 5% assuming a CVD rate in the control group of the study of 13.5% in 5 years. Taking into account a loss to follow-up of 15 at least 740 patients needed to be randomized.(16)

All analyses were conducted according to the intention-to-treat principle. Effects of treatment on study endpoints were estimated with the use of unadjusted Cox proportional-hazard models, involving survival time to the first relevant endpoint in any individual patient. Cox proportional-hazards models were applied to

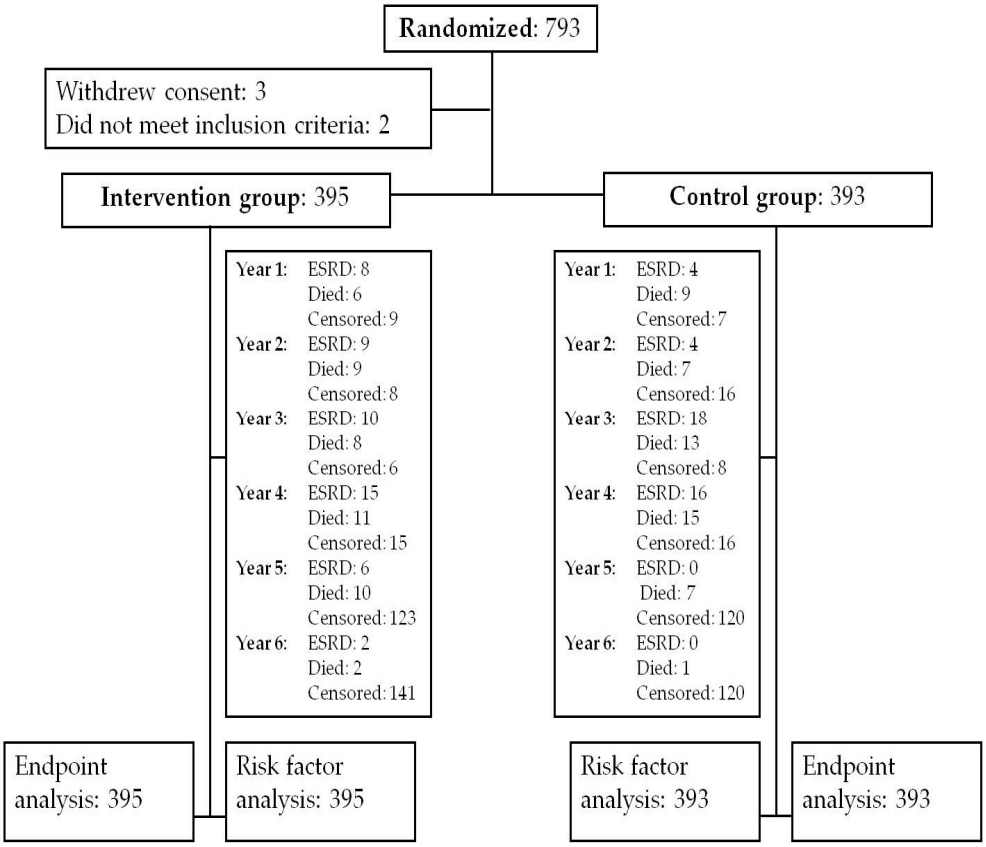
estimate the relative risk estimates and the corresponding 95% CI. Data for patients were censored at their date of death, date of last visit (those alive at the end of follow-up), or date when last known to be alive (those with unknown vital status). Differences in continuous and dichotomous variables between the two treatment groups during the follow-up period were estimated using linear mixed models (generalized estimating equations (GEE).(21) For that analysis, interest was in the mean difference over time in risk factor levels between treatment groups rather than the pattern of change. GEE analyses were performed using on trial measurements with adjustments for baseline measurements. All *p*-values were two-sided and *p*-values less than 0.05 were considered to indicate statistical significance. No adjustment for multiple statistical testing was made.(22) The homogeneity of treatment effects across subgroups (none of which were pre-specified) was tested by adding interaction terms to the relevant Cox models. All analyses were performed with the use of SPSS 17.0 (SPSS inc., Chicago, USA).
An independent data and safety monitoring committee reviewed the incidence of the primary endpoint in the two groups at regular three-month intervals using group sequential analysis.(23) The sequential analysis has been detailed elsewhere.(16)

Results

About 60% of patients deemed eligible by their physician and asked to participate in the study, actually participated and was included. Non-participation was because of reluctance to changes in drug therapy and inability of the patient to attend the required visits.
Between April 2004 and December 2005 we randomized 793 patients.(Figure 1) Three patients did not meet inclusion criteria and two declined participation

directly after randomization. Thus 788 patients were included in the study; 393 in the control group and 395 in the intervention group.

Figure 1. Enrollment, randomization, and follow-up of study participants.



Abbreviations: ESRD = end stage renal disease (either dialysis or transplantation)
Between year 5 and study end two additional patients in the intervention group had ESRD and two died. The total number of deaths does not add up to the numbers used in Table 4 because death occurring after ESRD or lost to regular follow up has been counted in Table 4 but not in Figure 1.

Characteristics were well balanced between groups apart from a history of CVD, which was more common and current smoking which was less prevalent in the intervention group.(Table 2) Mean follow-up time was 4.62 years (range 0.05 to 6.08).

Table 2. Characteristics of Participants at Baseline by assigned treatment.

Parameter	**Control group (n=393)**	**Intervention group (n=395)**
Age (yrs)	59.3 (12.8)	58.9 (13.1)
Gender (male) (%)	68	67
Race (Caucasian)	93	91
Nephrological diagnosis (%)		
Diabetic nephropathy	9	11
Renovascular	28	26
Glomerulonephritis/ interstitial nephritis	34	28
Congenital disease	13	11
Unknown	16	24
Kidney transplantation (%)	14	14
Prior cardiovascular disease by questionnaire (%)	25	33
Creatinine (mcmol/l)	181 (67)	182 (64)
eGFR (ml/min/1.73m^2)[a]	37.7 (14.0)	38.4 (15.2)
Office BP (mm Hg)	139 (22)/ 81 (11)	138 (20)/ 80 (11)
Oscillometric BP (mm Hg)	136 (21)/ 79 (11)	135 (20) / 78 (11)
Proteinuria (g/24 hr)[c]	0.3 [0.1-0.8]	0.2 [0.1-0.8]
LDL-cholesterol (mmol/l)	2.74 (0.90)	2.78 (0.95)
Haemoglobin (mmol/l)	8.2 (1.0)	8.2 (1.0)
History of DM (%)[b]	23	26
Phosphate (mmol/l)	1.10 (0.24)	1.10 (0.25)
PTH (pmol/l) [c]	9 [5-14]	9 [5-15]
Sodium-excretion (mmol/24 hr) [c]	150 [113-189]	148 [116-195]
BMI (kg/m^2)	27.2 (4.9)	27.0 (4.6)
Physical activity (%) [d]	60	57
Smoking (%)	24	19

Values are proportions, means with corresponding standard deviation, or median with inter quartile ranges, when appropriate.
Abbreviations: eGFR= estimated glomerular filtration rate, BP = blood pressure, DM= diabetes mellitus, PTH = parathyroid hormone, BMI = body mass index
[a] Based on the MDRD formula
[b] History of diabetes mellitus defined as using blood glucose lowering medication or fasting glucose >7.0 mmol/l.
[c] median [25th -75th percentile]
[d] adherence to Dutch physical activity guideline

Table 3. Effects of strict implementation of the guidelines on various risk factors during follow-up using the intention to treat principle with complete follow-up.

Risk factor	Mean levels at baseline		Mean level during follow-up[a]		Mean difference[a]	SE	*p*- value for difference
	Control	Intervention	Control	Intervention			
Systolic office BP (mm Hg)	139	138	135	132	-3	0.77	<0.001
Diastolic office BP (mm Hg)	81	80	79	77	-2	0.45	<0.001
Systolic oscillometric BP (mm Hg)	136	135	132	129	-3	0.61	0.002
Diastolic oscillometric BP (mm Hg)	79	78	77	75	-2	0.49	<0.001
LDL cholesterol (mmol/l)	2.74	2.78	2.50	2.39	-0.11	0.04	0.008
HDL cholesterol (mmol/l)	1.31	1.31	1.26	1.29	0.03	0.019	0.15
Triglycerides (mmol/l)	1.89	1.80	1.89	1.74	-0.145	0.06	0.009
Proteinuria (gr/24/h)	0.81	0.76	0.77	0.65	-0.117	0.06	0.04
Hemoglobin (mmol/l)	8.2	8.2	8.0	8.1	0.096	0.04	0.03
Phosphate (mmol/l)	1.11	1.10	1.15	1.13	-0.01	0.016	0.43
PTH (pmol/l)	11.7	10.8	13.7	13.3	- 0.38	0.67	0.57
HbA1c (%)	6.1	6.1	6.3	6.3	-0.003	0.05	0.96
BMI (kg/m^2)	27.2	27.0	27.0	27.1	0.02	0.11	0.88
Sodium excretion (mmol/day)	155	156	155	156	1.15	3.12	0.72
Physical activity (%)[b]	60	57	58	62	3.8	2.6	0.15
Smoking (%)	24	19	14	14	0.0	0.007	0.73
No. antihypertensive drugs	3.0	2.9	3.04	3.16	0.12	0.06	0.04
Use of ACEi and/or ARB (%)	78	81	85	87	2.6	1.4	0.07
Statin use (%)	63	67	76	80	4.7	1.55	0.002
Anti platelet drugs (%)[c]	39	45	57	67	9.6	2.4	<0.001
Glucose lowering drugs (%)	19	21	21	20	-0.03	1.17	0.73
Vitamin D (%)	24	22	41	46	4.6	2.0	0.02
Phosphate binders (%)	13	9	18	16	1.3	1.5	0.14

Abbreviations: BP = blood pressure , PTH = parathyroid hormone, BMI = body mass index, ACEi = ACE inhibitor, ARB = Angiotensin Receptor Blocker

[a]mean difference over time in risk factor levels between treatment groups obtained through GEE analyses using the on trial measurements with adjustments for baseline measurements. Complete follow-up means that all individuals have been followed with respect to the risk factor measurements also when they suffered a non fatal event or received kidney transplant or kidney replacement therapy

[b] adherence to Dutch physical activity guideline, [c] in those not using oral anticoagulant drugs treatment at baseline.

Figure 2. Change in oscillometric blood pressure (left) and LDL cholesterol (right) in both the intervention (black symbols) and control group (white symbols) during the first 5 years of the trial.

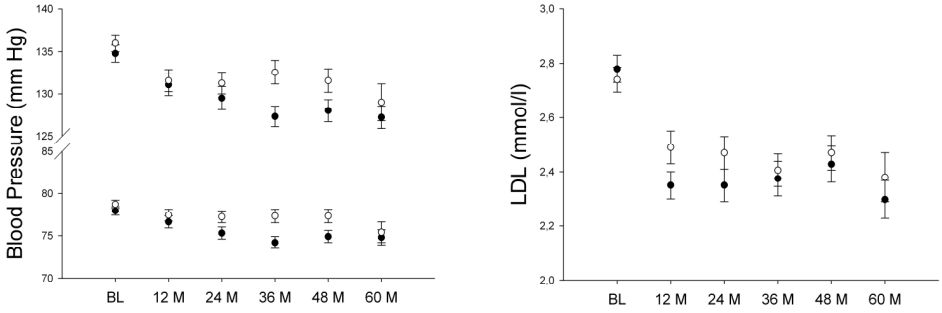
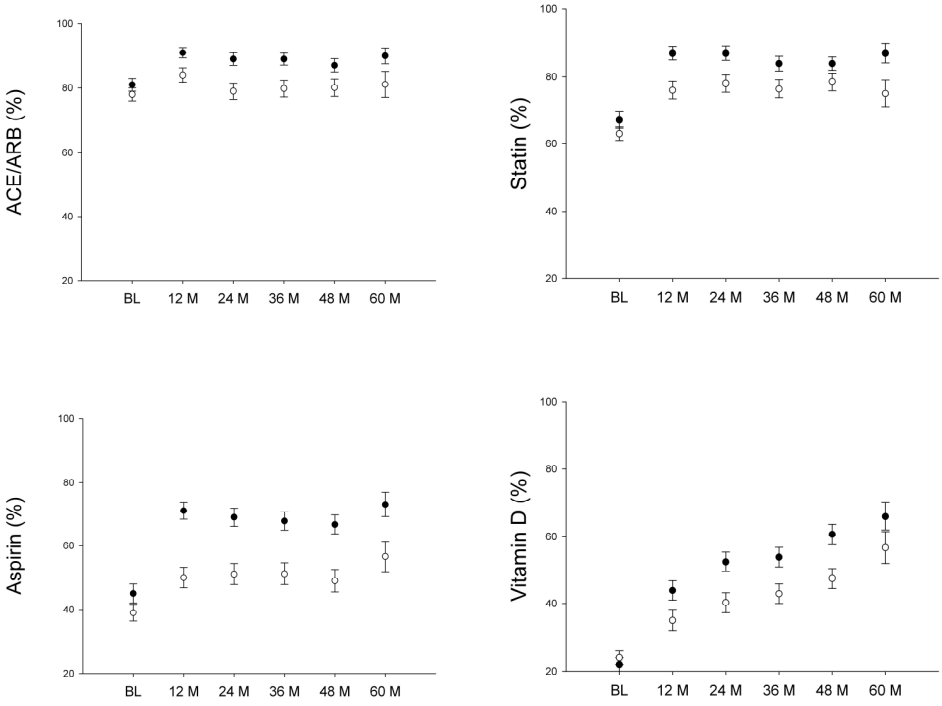


Figure 3. Percentage of patients using Ras inhibitors (upper left), statins (upper right), platelet aggregation (among those not on oral anticoagulants at baseline) (lower left) and vitamin D (lower right) in both the intervention (black symbols) and control group (white symbols) during the first five years of the trial.

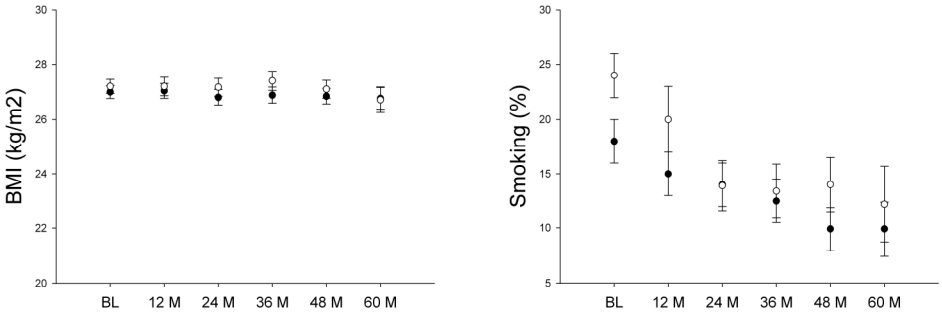


Effect on targeting risk factors

During follow-up mean office BP was significantly lower in the intervention group (132/77 mmHg) than in the control group (135/79 mmHg). Similar differences were found for oscillometric BP measurements.(Table 3) Significant differences were found for LDL cholesterol (-0.11 mmol/l), triglycerides (-0.15 mmol/l), hemoglobin (+0.01 mmol/l), anemia (-2%), proteinuria (-0.12 gr/24h) and use of vitamin D (or analogs) (+4.6.%), aspirin (+10%) and statins (+4.7%).

The number of antihypertensive drugs was higher and increased more in the intervention group (3.16 vs 3.04; p=0.04). Use of ACE-inhibitors and/or ARBs showed a trend of increased use in the intervention group (+2.6%; p=0.07). No differences were found for smoking, body weight, sodium excretion, physical activity or glycaemic control.(Table 3) The magnitude of the differences was small, despite its statistical significance.

Figure 4. The change in body mass index (left) and current smoking (right) in both the intervention (black symbols) and control group (white symbols) during the first five years of the trial.



In the control group similar beneficial trends were seen, leading to smaller differences between treatment arms. This is illustrated by the oscillometric BP data and the rapid increase in use of lipid lowering drugs and the use of platelet aggregation in both treatment groups just after randomization.(Figure 2 and 3) Identical patterns of changes in lifestyle factors were observed in both treatment groups for body mass index and current smoking.(Figure 4)

Effect on endpoints

A total of 80 participants had a major nonfatal or fatal CVD event during follow-up. Intensive control did not reduce the rate of the composite endpoint (21.3/1000 person-years in the intervention group versus 23.8/1000 person-years in the control group; hazard ratio 0.90 [95% CI 0.58, 1.39], $p = 0.62$).(Table 4)

The DSMB also reported their results for the primary endpoint applying sequential analysis (0.91[95% CI 0.59, 1.44], $p = 0.71$). No statically significant differences were found in secondary event outcomes, including end stage renal disease (dialysis and/or transplantation) (28.6 versus 34.4/1000 person-years; HR 0.83 [95% CI 0.57, 1.20], p=0.32). Subgroup analyses for baseline parameters such as age, gender, BP, baseline MDRD, previous transplantation, and previous CVD history showed no heterogeneity for the composite endpoint (all p- values for the interaction terms > 0.20).

Number of visits

The number of visits/year during the first two years was significantly higher in the intervention group than in the control group (7.2 versus 4.7; p<0.001). The number of physician visits in the intervention group was however significantly lower than in the control group (2.8 versus 3.7; p<0.001).

Table 4. Relative effects of strict implementation of the guidelines on all pre-specified primary and secondary outcomes.

Outcome	**Control**		**Intervention**		***p*-value for difference**	**Hazard ratio[a]**	**Lower 95% CI**	**Upper 95% CI**
	No. events	Personyears	No. events	Personyears				
Composite[b]	42	1767	8	1787	0.62	0.90	0.58	1.39
(Non)fatal AMI	11	1797	12	1813	0.85	1.08	0.48	2.45
(Non) fatal cerebrovascular disease	15	1781	12	1805	0.54	0.79	0.37	1.69
Fatal CV event	25	1812	23	1830	0.75	0.91	0.51	1.61
All cause mortality	52	1812	46	1830	0.52	0.88	0.59	1.30
ESRD	59	1714	50	1746	0.32	0.83	0.57	1.20
CABG	11	1784	12	1804	0.86	1.08	0.48	2.44
PTCA	16	1772	21	1790	0.40	1.30	0.68	2.50
Amputation	4	1808	6	1822	0.53	1.49	0.42	5.29
CHDplus[c]	31	1743	36	1761	0.57	1.15	0.71	1.86

Abreviations: AMI = acute myocardial infarction, CV = cardiovascular, ESRD = end stage renal disease defined as transplantation or dialysis, CABG = coronary artery bypass grafting, PTCA = percutaneous coronary angioplasty; CHDplus = coronary heart disease plus

[a] based on unadjusted Cox proportional hazards models using intention to treat principle.

[b] non fatal AMI, non fatal stroke, fatal CV event (whatever comes first);

[c] non fatal AMI, fatal coronary event , CABG, PTCA(whatever comes first);

Discussion

In our study we evaluate the effect of nurse practitioner assisted care of patients with CKD, targeting multiple risk factors. Compared to the control group we observe in the intervention group statistically significant better BP control, lipid management, less proteinuria and an increased number of antihypertensives, statins, aspirin and active vitamin D. Lifestyle interventions are ineffective. Intensive control does not reduce the rate of the composite endpoint of CVD mortality, myocardial infarction and ischemic stroke nor the incidence of either dialysis or transplantation.

Several trials evaluated the effect of nurse practitioners support in attaining treatment targets. Most studies were conducted in patients with diabetes(13;24-27) or patients with a high CVD risk score(28-32), and showed improvement in the management of some risk factors. In general, medication dependent risk factors such as BP and cholesterol were positively changed although in many studies beneficial effects were limited to only one of two risk factors.(13;24;26;27;29;32) Our study clearly shows that a nurse assisted intervention improves treatment in patients with CKD with respect to pharmacotherapy, BP, proteinuria and lipid metabolism. Our data agree with the Steno 2 study by Gaede et al.(13) In patients with diabetes mellitus II they observed improvement in BP, cholesterol, glycaemic control and aspirin use.
A recent randomized trial (CanPrevent) in 474 patients with CKD compared nurse coordinated care under nephrologist supervision with general practitioner care during two years.(33) They found no effect on risk factor control (BP, LDL cholesterol, serum phosphorus) and no reduction in clinical endpoints.

The contrasting results between the trials may be explained by differences in patient characteristics. CanPrevent included patients based on laboratory data procured in community laboratories, whereas our patients were under active nephrology care. Therefore Can Prevent included predominantly elderly patients, the majority being female, with better preserved kidney function, less proteinuria and at baseline very good BP control (130/74 mm Hg) and low LDL cholesterol. Most patients had non progressive kidney disease, and a relatively low CVD risk. Our study, which includes mostly patients with more severe kidney disease, clearly shows that risk factors can be positively influenced by nurse practitioner care. Still, although our study has a longer follow-up (4.62 vs 2 years) and includes patients with a much higher risk (CVD events are 5-fold higher and the incidence of ESRD is 10-fold higher), we also do not observe a significant effect on clinical endpoints.

Previous studies showing benefit of a lifestyle intervention were mostly targeted at a single risk factor.(34-37) Recent reports in preventive medicine have illustrated the difficulties in reaching any relevant benefits in studies involving multiple health behavior change. Effects, if any, mostly were limited in size.(31;38;39) Moreover other studies showed no benefit of a nurse practitioner intervention in body weight, smoking or physical activity.(30-32) Our results are in line with these studies and similar to the effects observed by Gaede et al.(40) Their multifactorial intervention showed no beneficial effect on weight, smoking or physical activity. Only a few studies compared the effect of single versus multiple intervention and all were targeted at both physical activity and nutrition.(41-43) Some showed superiority of a single intervention, while the other studies showed better results in the multiple intervention group.(41-43) A recent review concluded that single behavior interventions were more effective than multiple interventions in

promoting physical activity and changing dietary behavior.(44) These authors suggest that the number of possible choices may overwhelm the participants. Also, in our trial this may be relevant, since we have formulated 11 treatment targets for our patients.

At the start of the study, both patients and their physicians were informed about the existing guidelines and the goals and aim of the study. Apparently this influences physician care in the control group, as is indicated by the improvement in BP, lipid management and medication use.(Figures 2-3) These effects are mostly explained by more intensive drug treatment. The improvement in quality of care in the control group has partly obscured the potential benefits of the nurse led intervention explaining the small differences between the intervention group and the control group. This phenomenon known as contamination bias has been described in detail before and in retrospect should have lead to cluster randomized comparison rather than a individual participant randomized comparison.(45)
The differences in control of cardio-vascular risk factors in our study do not result in better CVD outcome in the intervention group. This is in contrast to the findings of Gaede et al.(13) Compared to our study however, patients in that study had higher BP and higher serum cholesterol at baseline. As a consequence, larger improvements in BP (systolic 11 mmHg, diastolic 4 mmHg), and LDL cholesterol (0.8 mmol/l) could be obtained. They also noted a larger difference in the use of aspirin between treatment groups (31%). Additionally, the study of Gaede consisted of patients with diabetes mellitus type II, and intensive treatment had a large impact on glucose regulation (HbA1c 7.9% on intensive therapy versus 9% in control). Finally in contrast to our design, the control patients in the Steno study remained under the care of a general practitioner, whereas all study patients were

taken care of by a study team led by nurse practitioner and internists in a highly specialized diabetes clinic.

The effects of an intensive treatment regimen in 200 patients with CKD stage IV and V, of whom 65% was on dialysis at the start of the study were reported by Isbel et al.(46) They showed a reduction in BP of -6.7/-3.8 mmHg and 0.4 mmol/l lower LDL cholesterol. After a follow-up of 2 years they failed to demonstrate differences in mortality CVD events or in surrogate endpoints such as intima media thickness.

The absence of a significant treatment effect in our study may be explained by several factors. First, the incidence of the primary endpoint is somewhat lower than expected (13.5%). This limits our ability to detect difference between groups. In the recent KDIGO CKD Prognosis Consortium analysis, the incidence of CVD events in our study is among the lowest among the 10 included cohorts.(19) Secondly, the magnitude of the differences observed between the treatment groups may have been too small to result in differences in events rates between the groups, potentially due to contamination bias. Based on the meta analyses on BP lowering and lipid lowering a difference in systolic pressure of 3.0 mmHg would result in a 6% reduction in coronary heart events, and a difference of 0.1 mmol/l in LDL in a 2% reduction of CVD events between the groups.(47;48) Our trial is not powered to detect such a small effect size. Yet, our 95% interval around the observed effect size includes this estimate.(Table 4)

Finally, recent studies have cast doubt on the efficacy of some of our interventions. There was no benefit of intensive BP or glucose lowering in otherwise reasonably well controlled patients in some recent large intervention trials.(49;50) Since BP at baseline in our study was (relatively) low, the impact of a further decline on the outcome may be small.

Although our study fails to demonstrate a significant improvement in CVD outcome in the intervention group, the support of the nurse practitioner results in at least equal and for some risk factors even better quality of care. We do not observe any adverse effects of the addition of the nurse practitioner. The number of physician visits was lower in the intervention group. The results are therefore supportive of a view that nurse practitioner care (using strict guidelines and supervision) can adequately substitute specialist care. This is an important notion of our study in view of the increasing incidence of patients with CKD, the required intensified treatment and a nephrologist workforce that may not be able to expand enough.(51;52) Our study suggests that nurse practitioners can assist in the care of CKD. Our study is not intended to evaluate substitution of physician care by nurse practitioner care, and the protocol does not include the registration of the duration and content of the visits. Therefore, we cannot judge the cost effectiveness of our intervention. To adequately appreciate the financial consequences of added nurse practitioner care a formal cost effectiveness analysis should be performed in a new study. To make this substitution cost-effective it is of course important to take into account the number and duration of contacts the nurse practitioners have in comparison with the specialist.

A formal cost effectiveness study was done in CanPrevent.(53) This analysis concluded that nurse coordinated care with nephrologist support reduced costs as compared to general practitioner care. It appeared that the difference in costs between the groups was totally driven by a lower number and shorter duration of hospitalizations in the intervention group. Unfortunately, such data are lacking in our study.

Conclusion

In this randomized study in 788 outpatients with CKD and a mean follow-up of 4.62 years, intensive treatment with the aid of nurse practitioners resulted in better control of some risk factors, but did not reduce the incidence of myocardial infarction, ischemic stroke or CVD death. Targeting multiple behavioral lifestyle changes was ineffective.

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Chapter 5.

Summary and perspectives

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Arjan D. van Zuilen

Summary

Patients with chronic kidney disease (CKD) have a markedly increased risk of dialysis, cardiovascular disease and mortality. Several guidelines have been published that address risk factor management. It is assumed that implementation of guidelines reduces this risk, However, this was not studied in patients with CKD until recently.(1)
The study described in this thesis questioned if the added support of nurse practitioners would improve risk factor management and reduce cardiovascular risk in patients with CKD.

Chapter 1
Chapter 1 discusses the rationale of the study, provides details of the study design, and focuses on the approach of the nurse practitioners toward lifestyle management. The assumption that added nurse practitioner support could be beneficial is based on the idea that doctors in their daily practice do not have enough time to discuss the multiple treatment goals with a patient. We envisage that additional care provided by a specialized nurse can be of benefit in multiple ways.
Firstly, through the mechanism of addition. Nurse practitioners have more time to discuss various issues and are also able to contact the patient more often and in different ways. Moreover they are specifically trained in lifestyle improvement, an often neglected issue in daily physician care. There may even be an effect on patient compliance because the interaction between the nurse and the patient is of a different nature than the interaction between doctor and patient.
Alternatively, nurse practitioner care may partly substitute or replace specialist care. If the nurse practitioners provide appropriate care to patients with CKD, the

addition of nurse practitioner to the team will increase the numbers of patients that can be treated by a nephrologist.

Chapter 2

In this chapter we show whether the assumption of the study holds. Improving the implementation of guidelines is only possible if in routine, daily care patients do not meet the targets as formulated in the guidelines. Although data from North-American and European cohorts.(2;3) already showed that treatment targets are often not met, this also has to be established in our own patient cohort. Table 1 illustrates the quality of risk facts management in our patient as compared to other studies.

Table 1: Overview of uncontrolled risk factors in studies in patients with CKD or coronary heart disease.

Factor	This study	De Nicola(3)	Tonelli(2)	Euro-aspire Non-diabetics(4)	Euroaspire diabetics(4)
BP	63%	88%	30%	75%	78%
Proteinuria	21%	35%	65%	Na	NA
Lipids	52%	58%	28-43%	79%	75%
Smoking	23%	11%	23%	22%	17%
BMI	67%	>50%	NA	78%	87%
uNA	83%	81%	NA	NA	NA

Numbers reflect the percentage of patients with risk factors levels above the defined target.
BP= blood pressure, BMI= Body mass index>25 kg/m^2, uNA= Urinary sodium excretion.
This study definitions: blood pressure >130/85mmHg, proteinuria>0.5g/day, lipids: LDL >2.6mmol/l, uNA>100mmol/24hr.
De Nicola definitions: blood pressure >130/80mmHg, proteinuria >1g/24 hr, lipids: serum total cholesterol >190 mg/dl, uNA >100mmol/24 hr.
Tonelli definitions: blood pressure > 140/90 mm Hg, proteinuria>1g/24 hr, lipids: serum total cholesterol >218 mg/dl or LDL > 116 mg/dl
Euroaspire definitions: blood pressure >130/80mmHg, lipids: LDL-cholesterol>2.5 mmol/l, BMI > 25 kg/m^2.

It is evident that at the start of the study a considerable number of patients has uncontrolled risk factors. Our data are in close agreement with the literature reports.

Further analysis of the data reveales that the participating centers differ with respect to achievement of treatment goals. This difference persists after adjustment for patient and center characteristics. Therefore, we conclude that these differences must be attributed to differences in the way doctors perform cardiovascular risk management. There are several possible explanations:

- Focus: As the physician usually has only 10 minutes per consultation, he can not discuss all risk factors. He makes a selection.
- Guidelines: For blood pressure alone, there were five applicable guidelines in 2004 for a patient with CKD; although they had more or less the same goals the sole number may have caused confusion.
- Therapeutic inertia: The doctor sometimes does not address a certain risk factor despite the fact that it is not optimally treated, e.g. because the patient already has a lot of medications or because during the consult already other interventions were performed and the physician decides to pursue no further changes during that specific visit.

Chapter 3

The ability to perform certain behaviors, including self-management, is mainly influenced by the belief that someone is actually able to execute that behavior. This belief is called self-efficacy.(5) Judith Wierdsma (nurse practitioner in Masterplan) showed in chapter 3, that she can measure self-efficacy using a validated questionnaire. She also shows that she is able to improve self efficacy in a subgroup of patients in the MASTERPLAN intervention group compared to a control-group, by discussing the believes of the patients with regard to therapy

adherence. Thus, nurse practitioners can modify self-efficacy, which is a driving force behind self –management. This may be important for the successful application of the technique of motivational interviewing.(6;7) Whether this translates in improved lifestyle is addressed in chapter 4.

Chapter 4

After two years patients coached by a specialized nurse have lower blood pressure and lower LDL-cholesterol than patients in the control group. Also, the patients in the intervention group use antihypertensive drugs, statins, aspirin and active vitamin D more often. The extra support by the nurse practitioner has no effect on smoking cessation, body weight, physical activity and dietary salt intake. Of note, when compared to baseline, quality of treatment also improves in the control group, although to a lesser degree than in the intervention group.

The observed differences in blood pressure between the intervention group and the control group persist for the remainder of the study (approximately five years). Similarly, differences persist for cholesterol, proteinuria, anemia and the use of above mentioned drugs. With longer follow-up, no benefits are seen for smoking, weight control, physical activity and salt intake.

The intervention does not reduce the incidence of cardiovascular events, nor does the need for renal replacement therapy decrease.

Perspectives

Although MASTERPLAN failes to demonstrate a reduction in end-points in the intervention group, our study provides important information for the treatment of patients with CKD.

Center differences

Analysis of the baseline data clearly illustrates that there are differences between centers with respect to the achievement of treatment goals. Since these differences persist after extensive statistical adjustments we hypothesize that the physician and his/her attitude towards treatment goals is an important explanation. This hypothesis is supported by the results presented in chapter 4.1. Here we show that in the intervention group the differences between centers largely disappear.
This can well be explained. All specialized nurses are uniformly trained and all apply the same guidelines and have more time to address multiple risk factors. The nurse practitioners also had meetings every 4-6 months, which provide opportunities for continued training and discussion. This makes therapeutic inertia less likely.
An important conclusion of our study is that despite the apparent homogeneous healthcare situation in our country with regard to insurance, access to healthcare facilities and sociodemographic build up, the quality of care is eventually also influenced by the physician and this does cause measurable differences in quality.een physicians. These differences can be reduced by providing guidelines and making a team responsible for patient care. We suggest that centralised training is important.

Contamination bias

In both study groups the treatment of cardiovascular risk factors improve. This may be the consequence of a general improved awareness in recent years of the increased cardiovascular risk in patients with CKD . However it may very well be that this is a consequence of study design. It is well known that control groups do improve in a randomized clinical trial.(8) Usually it is assumed that the motivation of a patient to participate in a trial also leads to a healthier lifestyle or stricter adherence to medication. Because of the design of our study, additional factors may come into play. The same physician who supervised the nurse practitioner also saw control group patients on a regular basis. It is very likely that this has influenced risk factor management in the control group.

This is known as contamination bias. It has been described in detail before and in retrospect should have lead to cluster randomised comparison rather than a individual participant randomised comparison.(8) In view of the reported differences between centers, cluster randomisation would have required a large number of participating centers, making the study more expensive.

If contamination bias indeed is a major factor in the improvement of the control group our study illustrates that if prompted by a strict protocol, physicians can improve treatment goals formulated in guidelines beyond their performance in daily practice.

Lifestyle

We hypothesize that specialized nursing care will be of particular benefit by helping the patient in improving lifestyle. Clearly, our study failes to show such an effect . Several aspects need to be considered.

Firstly our intention was to obtain a long-term lifestyle improvement. Actually there is only very limited data with regard to long-term lifestyle improvement (i.e.

longer than one year) and rarely beneficial changes are observed.(9;10) The study by Gaede et al. did also not show long term benefit.(11) Therefore in retrospect we would have been one of the first to report long term lifestyle improvement, if we had succeeded.

The earliest time point of our analysis is at one year after study start. Theoretically, it is possible that our intervention had short term effects which had already disappeared at one year and therefore have been missed. We consider this very unlikely.

There are also some factors that may have affected our lifestyle intervention. CKD is a silent disease, and treatment mainly consists of preventive measures. CKD patients usually do not feel ill as a consequence of their kidney dysfunction until dialysis is approaching. It is therefore likely that CKD patients are less motivated to ameliorate their lifestyle than patients who have experienced a severe event such as a myocardial infarction or stroke. This does not only pertain to the motivation to improve some aspects of lifestyle but also to the vital part of motivational interviewing namely that a successful change in one lifestyle factor will pave the road for other lifestyle improvements. It is uncertain if CKD patients indeed are motivated to strive toward a second goal if the first has been achieved. This possible lack of motivation could very well be the most important reason for the lack of change observed, although we have no data to substantiate this assumption.

Another factor was earlier mentioned by Jacobs et al.(12) In a multifactorial intervention the number of possible choices may overwhelm the participants, thus reducing the efficacy. This mayalso be relevant in our study, since we formulated 11 treatment targets for our patients, four of which are to be considered lifestyle interventions. There are two separate effects within this factor. Firstly the patient is never finished. If one goal is achieved the next goal is already brought forward

(because only 2% of patient in the entire cohort met 10 or more out of 11 goals at study start). This may adversely affect the patient's motivation. Secondly some lifestyle interventions may be conflicting. Weight gain after smoking cessation is a well known phenomenon but clearly conflicts with efforts to achieve relevant weight loss. Certainly when one person gives these apparently conflicting advices this may turn out to be counterproductive.

A third point may be that our lifestyle intervention is not intensive enough. Successful interventions often combine a period of inpatient guidance with intensive outpatient follow-up.(9) Our study is primarily based upon the assumption that the patient are motivated enough to change his or hers lifestyle via self-management.(5) Therefore in our design there is no place for such a firm intervention.

Finally one can wonder if the specialized nurses are trained adequately and address lifestyle issues prominently during their contacts with the patients. All nurse practitioners were trained uniformly before start of the study and particpate in frequent refresher courses on lifestyle management and motivational interviewing. The nurses consider themselves well equipped to address lifestyle issues and to coach patients. Whether additional training improves their self-efficacy and results remains uncertain however. Unfortunately we did not specifically measure the time spent on health related behaviour during outpatient visits.

Currently we do not know if there are subgroups within the MASTERPLAN study who did improve on some aspects of lifestyle. Additional subgroup analyses will have to be performed. Several groups are of interest.

- Patients who are on the brink of starting dialysis can postpone dialysis if adequately coached.(13) Multidisciplinary care (not necessarily targeted at lifestyle-improvement) also positively affects mortality and

hospitalizations in the first year after dialysis.(14) Therefore patients with worsening kidney function/ impending need for renal replacement therapy or with an eGFR below a certain threshold may be more inclined to improve lifestyle.

- Patients who had a cardiovascular event in their history are able to improve lifestyle.(10;15) This subgroup, consisting at the outset of the study of about 30% of patients, deserves special attention.
- If the hypothesis holds that motivation is increased and an improvement of lifestyle is more likely after a health related event, another group of particular interest are kidney transplant recipients. These patients have usually been on dialysis. There are currently no studies on lifestyle improvement in kidney transplant recipients available. There is some suggestion however that the lifting of lifestyle requirements caused by dialysis after transplantation has a negative impact on the self-efficacy of patients with regard to new health related behaviour.(16) Also in this cohort at baseline transplant recipients had a lower adherence to the physical activity guideline than untransplanted patients (49% in transplant recipients versus 60% in others; unpublished data) which can possibly support this. This group therefore may actually be less likely to improve lifestyle instead of more.
- The underlying kidney disease and other factors like age, gender and socio-economic status may also be of relevance.

What is the place of an effort to obtain lifestyle improvement by a nurse practitioner? Based upon the presented study lifestyle intervention using motivational interviewing as part of a Multifactorial approach on a group of moderate to severe CKD patients is ineffective.

There are three possible future strategies.

Firstly, one can decide to give no attention to lifestyle improvements. This will allow the specialized nurses to fully focus upon pharmacologically modifiable risk factors. Nurse supported care will be less costly.

Another approach is to make the nurse practitioner a case manager who decides in concordance with the patient on treatment goals. However different caregivers will address the chosen lifestyle factors. In this way the caregiver assisting in the lifestyle improvement is always fresh and unaffected by prior (unsuccessful) improvement attempts. Whether this approach will be effective remains to be established, there is no evidence to corroborate this strategy in patients with CKD.

A final strategy is to identify subgroups of patients in whom lifestyle improvement seems more likely to be successful and to concentrate a lifestyle effort on this subgroup. Although yet untested this seems a more effective and hopefully more beneficial way to apply the efforts of the nurse practitioner.

Cardiovascular endpoints

No difference can be established for cardiovascular endpoints as is shown in chapter 4.2. There are several possible explanations.

First, the incidence of the primary end point was lower (8.9% after 5 years) than expected (13.5%). This limits our ability to detect differences between groups. In the recent KDIGO CKD Prognosis Consortium analysis, the incidence of cardiovascular events in our study was among the lowest among the 10 included cohorts.(17) Whether this is a consequence of the standard of care in the Netherlands because of our primarily Caucasian population with ready access to reimbursed healthcare, the general attention awarded to CKD care from 2003 onwards or inclusion bias cannot be discerned.

A recent study in 500 Canadian patients with stage 3-4 CKD followed for two years compared family physician care with care by a specialized nurse under

supervision of a nephrologist. They failed to observe beneficial changes in BP and lipid profile and also did not note any difference on cardiovascular endpoints. Their conclusion was that on the outset of the study both intervention and control groups were fairly well controlled and that due to the slow progression of kidney disease during the study no meaningful difference on clinical endpoints could develop.(1)

Secondly, the differences in risk factor levels between the treatment groups may have been too small to result in differences in events rates between the groups. Based on the meta-analyses on blood pressure lowering and lipid lowering a difference in systolic pressure of 3.0 mmHg would result in a 6% reduction in coronary heart events, and a difference of 0.1 mmol/l in LDL in a 2% reduction of cardiovascular events between the groups.(18;19) Our trial was not powered to detect such a small effect size.

Both explanations however lead to the same conclusion. This study was severely underpowered and with additional patients and follow-up perhaps a benefit could have been established.

Additionally there are some other modulating factors to take into account. Recent studies have cast doubt on the efficacy of some of our interventions. There was no benefit of intensive blood pressure or glucose lowering in otherwise reasonably well controlled patients in some recent large intervention trials.(20;21) Since the blood pressure at baseline in our study is (relatively) low, the impact of a further decline on the outcome may be small or absent. Lowering of homocysteine and correction of hemoglobin levels to normal values with erythropoiesis stimulating agents were also found not to translate in improved cardiovascular risk .(22;23)

Perhaps other risk factors can be added or replace the offered intervention. It is possible that additional untargeted risk factors are of larger significance than the

risk factors that improved in our cohort. Possible candidates currently under investigation are for instance FGF-23, unactivated vitamin D, of which more and more so called pleiotropic effects are suggested, and uric acid.(24-26)
Finally also with regard to the main outcome, some subgroups may benefit from the intervention whereas others do not. However due to the limited number of endpoints, a post-hoc analysis will probably not be able to identify these subgroups.

Substitution

Patients receiving nurse practitioner care have similar or better control for every risk factor than patients under standard specialist care. This is an important observation in view of the increase in numbers of patients with moderate to severe CKD who require appropriate treatment.(27;28) In some countries it is calculated that the current number of nephrologists will not be sufficient to adequately manage this substantial increase.(29;30) No current prediction for the required workforce in the Netherlands is available, although it is likely that similar conclusions may be applicable in the Netherlands.
Our study offers a possible solution. Nurse practitioners who are under supervision of a nephrologist and use strict guidelines and flow charts, can adequately take over the care of patients with CKD. Patients need less visits with the specialist. In this fashion one specialist can increase his caseload considerably. There is ample support for this strategy in current practice based upon the fact that all nurse practitioners have continued to do their work after the study was finished and that in several other centers this concept of nurse practitioner care has been adopted.

To make this substitution cost-effective it is of course important to take into account the number and duration of contacts the nurse practitioners have in comparison with the specialist. In chapter 4.2 we show that patients in the intervention group were seen less by the physician. However, since substitution was not a formal goal of our study, the true effects of substitution of physician care by a specialized nurse on the number of contact moments and duration can only be analyzed in a formal evaluation of this concept. Interestingly the recently reported CanPREVENT study also performed a cost effectiveness analysis of their intervention and they concluded based upon less admissions and shorter hospital stays (variables currently not yet analyzed in the MASTERPLAN cohort) that intensive coaching was cost-effective.(31)

We conclude that the Masterplan study supports implementation of nurse practitioners in the day to day care of the CKD patient not because this has proven to improve cardiovascular outcome but because this improves control of cardiovascular risk factors and reduces differences between hospitals in an ever increasing patient population with also frequently changing treatment goals and risk factors. Additionally a lifestyle intervention should be reserved for subgroups that are likely to be open for a change in health behavior.

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Samenvatting in het Nederlands

Patiënten met chronische nierschade hebben een duidelijk verhoogd risico op dialyse, hart- en vaatziekten en sterfte. In de hoop deze risico's te verminderen zijn richtlijnen opgesteld waarin behandeldoelen zijn geformuleerd en adviezen worden gegeven voor de behandeling. Of het bereiken van de behandeldoelen mogelijk is en leidt tot werkelijke afname van renale en cardiovasculaire eindpunten is nooit onderzocht in patiënten met nierschade.
In dit proefschrift worden de resultaten beschreven van de MASTERPLAN studie, een gerandomiseerd onderzoek, met als doel na te gaan of betere implementatie van bestaande richtlijnen met behulp van gespecialiseerde verpleegkundigen leidt tot een vermindering van het cardiovasculair risico.

Hoofdstuk 1

In hoofdstuk 1 worden de achtergronden van de studie besproken en de behandeldoelen toegelicht. De gedachte achter de studie is dat de arts in zijn dagelijkse praktijk onvoldoende tijd heeft om de veelheid aan behandeldoelen adequaat met een patiënt te bespreken. Een gespecialiseerde verpleegkundige zou om meerdere redenen van toegevoegde waarde kunnen zijn.
De verpleegkundige heeft meer tijd om de verschillende behandeldoelen te bespreken en kan ook op meer en verschillende manieren contact met de patiënt opnemen. Bovendien is hij/zij beter geschoold in het begeleiden van veranderingen in leefstijl. Ook zou de de therapietrouw van de patiënt kunnen verbeteren omdat de interactie tussen de verpleegkundige en de patiënt van een ander karakter is dan de interactie tussen arts en patiënt.
Naast een toegevoegde waarde zou er ook sprake kunnen zijn van substitutie. Als de verpleegkundige adequaat de patiënten met chronische nierschade kan

begeleiden dan kan zij een aantal bezoeken van de arts overnemen. Hierdoor neemt het aantal patiënten dat één arts kan begeleiden toe.

Hoofdstuk 2

Hoofdstuk 2 toont aan dat veel patiënten hun behandeldoelen niet halen. Het aantal patiënten in de MASTERPLAN-studie dat een of meerdere behandeldoelen niet haalt verschilt niet van dat in andere bestudeerde patiëntengroepen. Opvallend zijn de verschillen in behaalde resultaten tussen de deelnemende centra. Dit kan verklaard worden door niet gemeten verschillen in patiëntkarakteristieken. De werkwijze van de arts lijkt echter ook een rol te spelen. Er zijn verschillende verklaringen mogelijk:

- Focus: Omdat de arts meestal maar 10 minuten per consult heeft kan hij niet alle risicofactoren bespreken. Hij maakt een selectie.
- Richtlijnen: Alleen al voor bloeddruk waren er in 2004 vijf verschillende actuele richtlijnen die je op een patiënt met nierschade kon toepassen. Deze lijken wel op elkaar qua behandeldoelen maar door het aantal kan er toch verwarring ontstaan. Dit staat nog los van verouderde versies die evt. door artsen gehanteerd konden worden.
- Therapeutische inertie: De arts doet soms niets aan een bepaalde risicofactor ondanks het feit dat deze niet optimaal behandeld is b.v. omdat de patiënt al veel medicatie heeft of omdat hij per consult maar een beperkt aantal beleidsaanpassingen wil uitvoeren.

Uit een analyse van de resultaten na twee jaar blijkt dat het verschil tussen de centra in de interventiegroep afneemt. Dit onderstreept dat de gevonden verschillen inderdaad samenhangen met verschillen in werkwijze van artsen.

Hoofdstuk 3

Het geloof in eigen kunnen is een belangrijke eigenschap om self-management na te streven. In hoofdstuk 3 wordt aangetoond door het onderzoek van Judith Wierdsma (een van de nurse pracititioners) dat het geloof in eigen kunnen bij patiënten met chronische nierschade gemeten kan worden met een gevalideerde vragenlijst. Zij laat ook zien dat dit geloof moduleerbaar is en dat dit het vertrouwen bij patiënten om hun medicatie conform de voorschriften in te nemen doet toenemen. Dit is waarschijnlijk belangrijk voor het succesvol gebruik van motivational interviewing als techniek.

Hoofdstuk 4

Na twee jaar blijkt dat de patiënten die extra begeleid worden door een verpleegkundige (interventiegroep) een lagere bloeddruk hebben en een lager LDL-cholesterol dan de controlegroep. Ook gebruiken de patiënten in de interventiegroep meer bloeddrukverlagende en cholesterolverlagende medicijnen en vaker aspirine en actief vitamine D. De extra begeleiding door een verpleegkundige leidt niet tot vaker stoppen met roken, meer gewichtsreductie, meer lichaamsbeweging of een lagere zoutinname in het dieet. Ook in de controlegroep verbetert de kwaliteit van de behandeling, maar het effect is minder groot dan in de interventiegroep.

Ook na 5 jaar is de bloeddruk van de patiënten die extra begeleid worden door een verpleegkundige nog steeds lager dan van patiënten die alleen behandeld worden door de eigen specialist. Verder scoren de patiënten die extra begeleid worden door een verpleegkundige ook beter wat betreft cholesterol, proteïnurie en bloedarmoede. Ook gebruiken deze patiënten vaker de bovengenoemde medicamenten. Wat betreft roken, gewicht, lichaamsbeweging en de hoeveelheid

zout die in het dieet werd gebruikt, wordt geen verschil gevonden tussen beide groepen.
De interventie leidt niet tot een minder voorkomen van hart- en vaatziekten. Ook is het aantal patiënten met terminaal nierfalen vergelijkbaar in beide groepen.

Hoofdstuk 5
De inzet van de gespecialiseerde verpleegkundigen leidt tot betere behandeling van bloeddruk en cholesterol. In de interventiegroep nemen de verschillen tussen de centra, zoals beschreven in hoofdstuk 2, af. Dit toont aan dat gemotiveerde zorgverleners in combinatie met strikte implementatie van richtlijnen de verschillen tussen ziekenhuizen kunnen verkleinen.
Niet alleen in de interventiegroep, maar ook in de controlegroep verbetert de behandeling van een aantal cardiovasculaire risicofactoren. De belangrijkste verklaring lijkt contaminatie bias. Doordat dezelfde arts die de nurse practitioner begeleidde ook controlegroep patiënten zag ging hij deze ook gelijk beter behandelen.
Om dit effect in het onderzoek te voorkomen hadden niet de patiënten maar de centra gerandomiseerd moeten worden. Daar zouden dan wel veel meer centra voor nodig zijn geweest.
Opvallend is het uitblijven van een verbetering van de leefstijl in de interventiegroep. In het onderzoek wordt gestreefd naar een verbetering op de lange termijn. In eerdere onderzoeken was al aangetoond dat dit erg lastig te realiseren is.
We denken dat de afwezigheid van verschillen verklaard kan worden door het feit dat patiënten met chronische nierschade zich niet ziek voelen en daarom niet heel erg gemotiveerd zijn om hun gedrag aan te passen. Een tweede verklaring is dat de verpleegkundigen te veel behandeldoelen moesten bespreken, soms ook met

tegenstrijdige effecten. Zo is het lastig om zowel te stoppen met roken als om af te vallen. Ten derde kan de interventie niet rigoreus genoeg geweest zijn. De uitvoering van onze interventie past echter heel goed bij de theorie van self-management en die staat zo'n strenge uitvoering niet toe.
Er kunnen best subgroepen zijn waar de leefstijl interventie wel succesvol was. Dit is echter nog niet geanalyseerd. Voorbeelden zijn: patiënten met een slechtere nierfuntie, patiënten met een doorgemaakt cardiovasculair event, patiënten met een niertransplantatie.

Dit resultaat van ons onderzoek leidt onherroepelijk tot de vraag of leefstijlinterventies een plaats heeft in het takenpakket van de gespecialiseerde verpleegkundige. Wij suggereren een aantal mogelijke strategieën.
Allereerst is het mogelijk om geen leefstijl interventie aan te bieden.
Daarnaast kan men er voor kiezen om niet alle behandeldoelen door één persoon te laten begeleiden. De verschillende leefstijl verbetertrajecten worden door specifieke specialisten uitgevoerd. Zowel bij zorgverlener als ontvanger bestaat dan geen misverstand over het doel van de contacten.
Tot slot lijkt het het meest zinvol om een leefstijlinterventie niet aan alle patiënten met chronische nierschade aan te bieden, maar alleen aan nader te identificeren subgroepen, waarbij dit soort interventies effect sorteren..

De verbetering in risicofactoren leidt nog niet tot minder cardiovasculaire sterfte, hart- en herseninfarcten.
Hiervoor zijn een aantal verklaringen. Allereerst is de incidentie van cardiovasculaire eindpunten in onze studie lager dan in vergelijkbare, in de literatuur gerapporteerde studies. Dit kan een weerspiegeling zijn van de algemene kwaliteit van zorg in Nederland. Een andere verklaring is dat de

kwaliteit van de behandeling ook verbeterde in de controlegroep (contaminatiebias).

De verschillen tussen de groepen voor bloeddruk en cholesterol zijn in elk geval zo klein dat geen grote, snel aantoonbare verschillen in hart- en vaatziekten mochten worden verwacht. In ieder geval was de studie eigenlijk te klein en/of te kort om een eventueel voordeel te laten zien.

Daarbij speelt nog dat van niet alle risicofactoren die in het onderzoek werden aangepakt de behandeling ook even belangrijk lijkt te zijn. Wellicht zijn er bovendien andere factoren die een grotere rol spelen in het risico op hart en vaatziekten die geen deel uitmaakten van de interventie.

Wij menen uit ons onderzoek te mogen concluderen dat gespecialiseerde verpleegkundigen de rol van de arts bij de begeleiding van patiënten met chronische nierschade gedeeltelijk kunnen overnemen. Dit kan veilig en verantwoord gebeuren, in de in MASTERPLAN gebezigde setting met directe begeleiding door een specialist, waarbij gebruik gemaakt wordt van zorgvuldig uitgewerkte, duidelijke stroomschema's.

Wij kunnen geen conclusies trekken over de kosteneffectiviteit. Hiervoor zal een specifieke kostenbaten analyse uitgevoerd moeten worden.

Over het geheel genomen heeft de MASTERPLAN studie een goed inzicht gegeven in het cardiovasculair risicomanagement bij patiënten met chronische nierschade in Nederland. Ook leidt het onderzoek tot nieuwe inzichten in de rol van gespecialiseerde verpleegkundigen in de zorg voor patiënten met chronische nierschade.

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Curriculum Vitae

Arjan Dirk van Zuilen was born on Juli 23, 1972 in Culemborg, the Netherlands. After graduating secondary school, the st Oelbertgymnasium in Oosterhout in 1990, he started his studies in biomedical health science in Nijmegen. Upon completion in 1994 he started his study in Medicine which was finalized in 1998. After two years as a resident Internal Medicine not in training in Sint Maartensgasthuis in Venlo, he started is specialist training in Internal Medicine with a two year residency in the Slingeland hospital in Doetinchem. After two years as resident in the Radboud University Nijmegen Medical Center he was admitted for a Nephrology fellowship in the University Medical Center (UMC) in Utrecht in 2004. This was also the start of a PhD program as a research physician for the Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners.

In 2002 he married his wife Angelique. In 2003 his son Wout was born and in 2005 his daughter Sarah . In 2007 as an internist and nephrologist he was accepted as a staff member of the UMC Utrecht in the department of nephrology and hypertension. From 2009 onwards he heads the kidney transplant unit of the UMC Utrecht. In 2011 he also finished the Basic Course Legislation and Organization for Clinical Researchers.

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