Optimising Chronic Kidney Disease management in primary care

Is shared care the answer?

Nynke Scherpbier-de Haan

The SHARING study and the CONTACT study were supported by a grant from the Dutch Kidney Foundation.

NIERSTICHTING
GEEFT TOEKOMST.

ISBN/EAN 978-90-9027410-2

Cover: 'Teamwork', door Ghislaine Collard, atelier Jans Pakhuys.

In atelier Jans Pakhuys werken kunstenaars met een verstandelijke beperking. Jans Pakhuys is onderdeel van de Amerpoort, Amersfoort.

Design/layout: Promotie In Zicht, Arnhem
Print: Ipskamp Drukkers, Enschede

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Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 7 juni 2013
om 11.00 uur precies

door

Nynke Dorothea Scherpbier-de Haan
Geboren op 1 oktober 1964
te Oegstgeest

Promotoren

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General introduction

BACKGROUND

Chronic kidney disease (CKD) is a substantial health problem.[1,2] A minority of patients with CKD will progress to end stage renal failure, resulting in a high personal and societal burden. An even greater concern is the association of CKD with a high risk of cardiovascular morbidity and mortality and with a reduction in life expectancy.[3,4] Early detection and treatment contribute to better patient outcome.[5,6] A discussion is ongoing of how and where to organise this care in an effective way.[7] Many factors point to primary care as the logical environment to detect and manage the majority of CKD patients.[8] At the same time, these very factors face the primary care organisation with a challenging complexity. This thesis aims to explore aspects of CKD management in primary care, whereby the connection with secondary care is incorporated.

The following factors considering CKD management contribute to both the essential position of primary care and the organisational demands:

A. **the high prevalence of CKD with resulting workload**: it is not possible and necessary to manage all patients with CKD in secondary care. Care should be given in a primary care setting where possible. To manage the workload well, the GP will have to delegate tasks to assistants and nurse practitioners. Collaborative care with nephrology should be sought at the appropriate time.

B. **the many co-morbid conditions** and associated multitude of health care providers in primary and secondary care: general practice is in the position to have an overview, but will have to take the responsibility to coordinate well.

C. **medication safety**: the dosage of drugs that depend on renal excretion should be adjusted and nephrotoxic drugs should be avoided. General practice has information on both medication use and renal function, but not always the knowledge to detect and solve all issues.

D. CKD is **a long-term, dynamic condition** which may be complicated by acute exacerbations. General practice, with it's integrated care and easy access, is a good setting to manage long-term conditions and to recognise 'acute-on-chronic' situations. This requires knowledge and alertness through all staff layers of the practice.

We present a clinical lesson on a patient in general practice to illustrate these factors[9]. Subsequently, the above mentioned aspects will be discussed in further depth, resulting in the aim and research questions of this thesis.

Mr A, an 81-year-old man, is known with hypertension and a moderately decreased renal function and has a history of heart failure, colon cancer, a TIA and gout. Due to watery diarrhoea and abdominal pain during the previous 24 hours the general practitioner made a home visit. There was no fever. The general practitioner observed nothing unusual during an examination. Three days later the out of hours general practitioner service was called because the patient could scarcely urinate any more. The patient had continued to take his medicine faithfully which consisted of lisinopril (20 mg once daily), amlodipine (10 mg once daily), atenolol (100 mg once daily), chlortalidone (12.5 mg once daily), acetylsalicylic acid (100 mg once daily), omeprazole (20 mg once daily), and diclofenac (50 mg as needed 3 times daily).

At the emergency department the internist saw a scarcely ill man with an ashen face. The blood pressure was 115/50 mmHg and the pulse 55 beats per minute. No abnormalities were found during a physical examination. The abdomen was non tender. Laboratory tests on admission revealed normal Hb, CRP, sodium and liver values. The serum creatinine (1183 µmol/l), potassium (6.5 mmol/l) and urea (55.7 mmol/l) values were elevated. Microbiological tests revealed negative blood, faeces and urine cultures. It appeared that one year before admission the creatinine had gradually increased from 130 µmol/l to 178 µmol/l (MDRD 34 ml/min/1.73m^2).

The clinical picture is compatible with an 'acute-on-chronic' renal failure, as a consequence of dehydration during gastroenteritis and the use of an ACE inhibitor, diuretics and NSAIDs. All antihypertensives and the diclofenac were suspended. The patient received a generous drip and glucose and insulin were administrated for the hyperkalaemia. The serum creatinine concentration decreased over 10 days to 151 µmol/l, after which the patient could be discharged in a reasonable condition. Of the antihypertensives only atenolol (50 mg once daily) was still given. One month after discharge the patient developed swollen feet. Under strict monitoring of renal function, diuretics were added and lisinopril was gradually resumed and increased to 40 mg daily. Six months after admission the patient was doing reasonably well. Serum creatinine concentration was 135 µmol/l (MDRD 47 ml/min/1.73m^2).

In the Netherlands, 5.3% of the general population has an MDRD-value below 60 ml/min/1.73 m^2.[10] Using data from the Nijmegen Biomedical Study, we calculated that in a typical general practice there will be about 40 patients who use RAAS inhibitors and who have an MDRD $<$ 60 ml/min/1.73 m^2.[11]

Within the group of patients with chronic reduced renal function who use a RAAS inhibitor, the elderly and patients with a reduced cardiac function have an increased risk of developing an 'acute-on-chronic' renal failure during fever or gastroenteritis.[12] Particular attention needs to be paid during warm summer days. Patients with atherosclerosis have a higher chance of a poor renal circulation because renovascular atherosclerosis will also be present. Use of diuretics and/or NSAIDs forms an additional risk.[13]

In our patient the creatinine values in the years prior to this hospital admission increased from 130 μmol/l to 178 μmol/l , which is equivalent to an estimated glomerular filtration rate (MDRD formula) of 34 ml/min/1.73 m^2. These are not uncommon values within general practice but these patients will not always be assigned a problem code 'chronic reduced renal function' in the diagnosis list in the electronic health record. And even if this would be the case, the practice assistant or general practitioner will probably not be alarmed straightaway if the patient phones and says that he/she has gastric flu or fever. Our patient had the following risk factors: chronic reduced renal function, ACE inhibitor use and diuretics use in combination with diarrhoea. This should have been a reason to check the creatinine and potassium and to adjust the medication. The NSAID use formed an additional risk for the development of acute renal failure.

RAAS inhibitors are often indicated for patients with chronic renal damage in order to prevent a further deterioration of the renal function and to reduce the blood pressure. However during intercurrent disease these should sometimes be temporarily reduced or suspended based on the clinical status and laboratory results.

A. High prevalence, necessity to organise care well

The prevalence of CKD is high: more than 13% in the general population in the USA and 6.8% in known patients in primary care in the UK.[1,14] The expectation is that, with ageing of the population and rising incidence of diabetes and hypertension, the prevalence will even rise further in the future.[1] Routine laboratory controls and default reporting of the estimated renal function by laboratories have added to CKD recognition in primary care.[15] Patients like Mr A will occur more and more in general practice.

Recommended interventions for CKD management are provided in guidelines[16-18]. Blood pressure and cholesterol lowering and reduction of proteinuria form the main goals of the guidance. General practitioners are in the position to carry out these guidelines, however treatment targets are often not met.[19-21] A lack of knowledge and confidence in CKD management may be the cause, but also scepticism concerning blood pressure targets.[22,23] Furthermore, guidelines are so time-consuming and of such a complexity that it is almost impossible to implement them in daily care.[24]

It is not clear yet which approach in organising care for CKD patients is most effective. Transferring knowledge and guidelines is a prerequisite, but that alone is not sufficient.[25] Of additional value could be the identification of patients from electronic patient records, computer decision support and collaborative care between general practitioner and nephrology.[21] A primary care based disease management program proved to be effective in an observational study, but the effectiveness of a multidisciplinary approach in primary care has not yet been proved in randomised trials.[26-29]

B. Multimorbidity

Patients with CKD often have co-morbidities: diabetes, hypertension, cardiovascular disease and anaemia.[30] Frailty could be added to these examples. Preferably, these patients should not have to travel to see different doctors for their different conditions.

Primary care is in a transition phase from demand-driven single problem care to pro-active care for patients with long-term conditions. Disease management programs for patients with diabetes and cardiovascular disease are effective and have evolved considerably.[31,32] If treatment of patients with multiple long-term conditions would be split up in a number of separate disease manage programs, the risk of fragmentation of care is considerable.[33] Primary care is in the position to integrate care and model guideline advice to fit the individual patient with complex unordered problems.[34] As there are many parallels in diagnosis and treatment of CKD patients with that of diabetes or hypertension-patients, it might be helpful to treat CKD patients in the same structure as patients with diabetes or hypertension.

C. Medication safety

Patients with impaired renal function are at increased risk of preventable drug related morbidity and preventable medication-related hospital admissions.[35,36] When renal function is reduced, the dosage of drugs that depend on renal excretion should be adjusted[37]. For example the dosage of digoxin should be adjusted to renal function to avoid the risk of digoxin toxicity.[35] Nephrotoxic drugs like NSAIDs should be avoided.[38,39]

Although primary care has the tools to monitor medication safety, many medication errors in relation to impaired renal function occur[40,41]. Many factors contributing to that can be identified. First, digital prescribing may warn for 'impaired renal function', but hardly ever takes the value of renal function automatically into account. Second, renal function is fluctuating over time, so in chronic medication the appropriateness of drug and dosage should be reconsidered on a regular basis. Third, the paradox is that drugs that are in essence beneficial for CKD patients, like RAAS inhibitors, can be harmful in specific situations (reduction of circulating volume). Finally, the balancing

between co-morbidities that compete for attention requires distinct craftsmanship[42]. The combination of impaired renal function, heart failure and gout like in Mr A is a typical Scylla and Charybdis situation.

As securing medication safety in patients with CKD is complicated, safety nets must be built in at different stages. The pharmacist might be of additional value in this process.

D. Dynamic condition

The management of chronic kidney disease is guided by the stage of the disease.[16] Change in renal function over time is an additional consideration in judging the severity of the disease.[43] In general practice, often series of creatinine measurements are available. The general practitioner should judge the course of renal function, proteinuria and blood pressure over time and relate the findings to medication changes and intercurrent diseases. These situations do not fit in the disease management program, but require integration and interpretation of information already available. This is not always easy in the hassle of daily practice. A structured presentation of historical data might help in getting an overview. Not only should the general practitioner have the knowledge, but also the practice nurse who sees the patient for an annual diabetes or hypertension control and the practice assistant who speaks to the patient on the phone in case of an intercurrent disease like gastro enteritis or fever.

AIM OF THIS THESIS

Exploring the chances and borders of CKD management in primary care implies knowledge about these patients and about the organisational possibilities to meet their needs. The general aim of this thesis was to explore these fields.

Research questions

1. What is the prevalence of known patients with chronic kidney disease in primary care?
2. What is quality of care for patients with CKD in primary care related to the guideline advice?
3. What is the prevalence of metabolic abnormalities in patients with CKD in primary care?
4. Would a shared care model between nurse practitioner, general practitioner and nephrologist, supported by a web-based consultation system, contribute to the care for patients with chronic kidney disease?

5. What is the feasibility of a web-based consultation between general practitioner and nephrologist?
6. What are issues in medication safety in patients with CKD and diabetes or hypertension? What could be the contribution of a pharmacist?

These questions form the structure of this thesis. Secondary research questions came on the way, but the basic question remained paramount: how could the organisation in primary care be structured in a way that CKD patients get the treatment that is indicated, preferably in their own environment?

OUTLINE OF THE THESIS

Chapter two describes the prevalence of CKD patients in primary practices in the Netherlands and the quality of care currently given compared to the Dutch inter-disciplinary CKD-guideline for primary care and nephrology.

Chapter three gives more detailed insight in patients with CKD in primary care regarding abnormal serum PTH, calcium and phosphate.

In chapter four we describe the results of our study that tested a shared care model for patients with chronic kidney disease in nephrology and general practice in a cluster randomized controlled trial.

When treating patients with CKD in primary care, consultation of a nephrologist in a digital environment maybe of value. In chapter five we describe the initial implementation of a web-based consultation process for patients with CKD.

In chapter six we assess the pharmaceutical problems in relation to renal function in older patients and the potential contribution of the pharmacist in that field.

Chapter seven comprises a validation study of 30-minute automated office blood pressure measurement compared to usual automated office blood pressure measurement.

Finally, in chapter eight the most important findings of the studies are summarised and discussed.

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2

Quality of care for patients with chronic kidney disease in primary care: opportunities for improvement. *A retrospective study*

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ABSTRACT

Purpose: Early detection and appropriate management of Chronic Kidney Disease (CKD) in primary care are essential to reducing morbidity and mortality. This study aimed to assess the quality of care (QoC) of CKD in primary healthcare and to identify related patient and practice characteristics, so improvement strategies can be based on these findings.

Methods: In this retrospective study, data were collected from 47 family practices (207,469 patients of whom 162,562 adults) in 2008–2011. CKD management of patients under care of their family physician(FP) was qualified using indicators derived from the Dutch interdisciplinary CKD-guideline for primary care and nephrology and included [1]monitoring of renal function, albuminuria, blood pressure and glucose, [2]monitoring of metabolic parameters, and alongside the guideline: [3] recognition of CKD. The outcome indicator was [4] achieving blood pressure targets. Multilevel logistic regression analysis was applied to identify associated patient and practice characteristics.

Results: Kidney function or albuminuria data were available for 64,102 patients. 9295 patients had CKD, of whom 8845 were under FP care. Monitoring of disease progression was complete in 43% of CKD-patients, monitoring of metabolic parameters in 2%, and blood pressure target was reached in 43.6%. FPs documented CKD in 31.7% of CKD-patients. High QoC was strongly associated with diabetes, and to a lesser extent with hypertension, male sex and rural practice location.

Conclusions: Gaps in care were found in all aspects of CKD management. As QoC was higher for patients participating in diabetes disease management programs, future CKD care may profit from embedment in comparable programs.

Trial registration: Nederlands Trial Register NTR2368

INTRODUCTION

Family physicians play a key role in the care of patients with Chronic Kidney Disease (CKD). Early detection and appropriate management of CKD is essential to reduce morbidity, mortality and disease progression. The number of patients that suffer from CKD is growing, as illustrated by the rise in community prevalence in the USA. Prevalence of CKD stages 1–4 rose from 10.0% in 1988-1994 to 13.1% in 1999-2004, using the definitions of CKD as proposed in the National Kidney Foundation's 'Kidney Disease Outcome Quality Initiative' (K/DOQI) guidelines.(1-3) Considering this increase in health care burden, a high level of primary care engagement in the management of CKD not only is convenient to the patient but also contributes to cost-effectiveness in health care.(4-6)

The K/DOQI guidelines (USA) and the National Institute for Health and Clinical Excellence (NICE) CKD guideline (UK) provide family physicians with recommendations on good CKD management, including monitoring of disease progression and strictly controlling cardiovascular risk factors.(3, 7) The Dutch interdisciplinary CKD-guideline for primary care and nephrology is similar to these guidelines, but incorporates age in its recommendations (Appendix table 1).(8-13)

Studies have shown that high standard CKD management attenuates and delays adverse outcomes such as progression to end stage renal failure, cardiovascular events, and disturbances in bone and mineral metabolism.(14-24) However, literature also notes deficiencies in the quality of care (QoC).(25-30) To our knowledge there has been no study that specifically addressed QoC in routine family practice for all stages of CKD. Our study aimed to analyze process and outcome indicators of CKD management in patients under care of their family physician, and to identify associated patient and practice characteristics. *Process* indicators reflect whether a caregiver executed specific health care activities, whereas *outcome* indicators reflect the effect of these activities on the health of the patient.(31) We hypothesized that our study would uncover gaps in care and reveal predictors of high QoC. Our data should enable development of better targeted improvement strategies.

METHODS

Recruitment of participants

This study used baseline patient data of family practices that participated in a cluster randomized controlled trial on the effect of web-consultation between FP and nephrologist on in-person referrals: the CONTACT study (Consultation Of Nephrology

by Telenephrology Allows optimal Chronic kidney disease Treatment in primary care, Netherlands Trial Registration code 2368). The CONTACT study recruited family practices during a CKD management course for family physicians in the eastern part of the Netherlands. Forty seven non-academic family practices signed up for participation. Data between 2008-2011 were analyzed from their registered populations' electronic medical records (n=207,469). In this retrospective study, we included all patients aged 18 years or older who met the CKD criteria: eGFR<60ml/min/1.73m^2 or albuminuria. Patients under secondary renal care were excluded from the analysis.

Classification of patients

The interdisciplinary CKD-guideline for primary care and nephrology provides guidance for the FP in selecting the best suited health care setting for patients with CKD, based on eGFR, albuminuria and age. These settings are: treatment in primary care, consultation of a nephrologist without referral, and referral to secondary care. We applied this classification to our cohort, resulting in a 'primary care' group, a 'consultation' group and a 'referral' group (Table 1). The guideline also provides group specific monitoring criteria. In the 'primary care' group this implied monitoring of disease progression, while the 'consultation' and the 'referral' groups additionally required monitoring of metabolic parameters (Appendix table 1). Serum creatinine measurements were either isotope dilution mass spectrometry (IDMS) traceable or subject to the Jaffé technique. Laboratories estimated renal function using the appropriate abbreviated Modification of Diet in Renal Disease (MDRD) equation for IDMS and Jaffé technique respectively.(32, 33) We defined microalbuminuria as an urinary albumin to creatinine ratio (ACR) of 2.5–25mg/mmol in men and 3.5–35mg/mmol in women. Higher ratios were considered to reflect macroalbuminuria. If an ACR was unavailable, we used urine albumin concentration with cut-off values >20–200mg/l for microalbuminuria and >200mg/l for macroalbuminuria. Patient age was set on the latest eGFR date.

Process and outcome indicators (Table 2)

We derived indicators from the evidence based interdisciplinary CKD-guideline for primary care and nephrology.(13) Included process indicators were: [1] monitoring of disease progression (assessment of eGFR or serum creatinine, albuminuria, glucose, and blood pressure); [2] monitoring of metabolic parameters(assessment of hemoglobin, calcium, phosphate, parathyroid hormone (PTH), serum albumin, and potassium), and alongside the guideline; [3] recognition of CKD in patients with an eGFR < 60 ml/min/1.73m^2 (separate entity on the episode list in the electronic medical record with International Classification of Primary Care (ICPC) code U99.01 for renal impairment). The outcome indicator was [4] achievement of blood pressure targets. To achieve blood pressure targets, the mean of the two latest measurements had to be <140/90mmHg.

Table 1 Classification of patients using the interdisciplinary CKD-guideline for primary care and nephrology

	Albuminuria			
	Not known	Normal	Microalbuminuria	Macroalbuminuria
Patients ≥ 65 years (*n* = 20.867)				
eGFR ≥ 60	8.488	5.653	893	74
eGFR 45 – 60	2.134	1.583	411	52
eGFR 30 – 45	642	420	195	46
eGFR < 30	181	43	33	19
Patients < 65 years (*n* = 43.235)				
eGFR ≥ 60	32.361	8.305	693	59
eGFR 45 – 60	894	595	70	16
eGFR 30 – 45	106	51	22	7
eGFR < 30	39	3	6	8

Classification of patients based on renal function, albuminuria and age. 'primary care group': treatment in primary care. 'consultation group': consultation of a nephrologist without referral. 'referral group': referral to secondary care. eGFR in ml/min/1.73m^2

Additionally, we analyzed blood pressures <130/80mmHg to allow comparison with existing literature.

Patient and practice characteristics

We extracted patient demographic and clinical data concerning date of birth, sex, co-morbidities and medication from the electronic medical record (Table 3). Patient age was categorized in ranges 18-45 years, 45-60 years, 60-75 years, and over 75 years old. Co-morbidities were defined by ICPC codes as a history of diabetes (T90), hypertension (K86,K87) and cardiovascular disease (K74-K77,K89,K90,K92).(34) We selected drug prescriptions issued during 2010 for medication shown in table 3 using Anatomical Therapeutic Chemical (ATC) codes for descriptive purposes only.(35)

Practice characteristics included practice type (solo-,duo- or group-practice), vocational training practice, practice location (urban or rural based on the Statistics Netherlands' Key figures postcode areas database of 2004), and General Practice Information System (5 different systems)(Appendix table 2).

Table 2 Performance on process and outcome indicators within 15 months prior to data extraction

Patient group	N	Monitoring of disease progression					Monitoring of
		renal function	albu-minuria	fasting glucose	blood pressure	complete	hemo-globin
Primary care group							
Age ≥ 65 eGFR ≥ 60 and micro-albuminuria	892	828	763	812	810	697 (78%)	
Age < 65 eGFR ≥ 60 and micro-albuminuria	693	593	556	584	545	467 (67%)	
Age ≥ 65 eGFR 45 – 60	4124	3416	1699	2624	3040	1571 (38%)	
Total primary care	5709	4837 (84.7%)	3018 (52.9%)	4020 (70.4%)	4395 (77.0%)	2735 (47.9%)	
Consultation group							
Age ≥ 65 eGFR 30 – 44	1237	1033	489	704	893	452 (37%)	699
Age < 65 eGFR 45 – 60	1547	1126	541	848	918	457 (30%)	623
Total consultation	2784	2159 (77.6%)	1030 (37.0%)	1552 (55.7%)	1811 (65.1%)	909 (32.7%)	1322 (47.5%)
Referral group							
Age ≥ 65 eGFR < 30	102	85	24	48	59	21 (21%)	73
Age < 65 eGFR 30 – 44	72	53	18	39	43	18 (25%)	40
Age < 65 eGFR < 30	13	10	0	4	6	0 (0%)	9
Macro-albuminuria	165	145	121	145	138	108 (66%)	68
Total referral	352	293 (83.2%)	163 (46.3%)	236 (67.0%)	246 (70.1%)	147 (41.8%)	190 (54.1%)
Total consultation and referral	3136	2452 (78.2%)	1193 (38.0%)	1788 (57.0%)	2057 (65.6%)	1056 (33.7%)	1512 (48.3%)
Total	8845	7289 (82.4%)	4210 (47.6%)	5808 (65.7%)	6452 (72.9%)	3791 (42.9%)	

Process- and outcome indicators are derived from the interdisciplinary CKD-guideline for primary care and nephrology. For each indicator, performance in the preceding 15 months is shown.

metabolic parameters						Recog-nition	Blood pressure targets	
calcium	phos-phate	PTH	serum albumin	potassium	complete		<140/90 mmHg*	<130/80 mmHg*
							279 (34%)	94 (12%)
							259 (48%)	85 (16%)
						1087 (26%)	1264 (42%)	485 (16%)
							1802 (41.0%)	664 (15.1%)
192	158	75	121	876	34 (3%)	722 (58%)	434 (49%)	199 (22%)
93	73	32	47	813	15 (1%)	325 (21%)	475 (52%)	151 (16%)
285 (10.2%)	231 (8.3%)	107 (3.8%)	168 (6.0%)	1689 (60.7%)	49 (1.8%)	1047 (37.6%)	909 (50.2%)	350 (19.3%)
24	16	5	16	72	2 (2%)	67 (66%)	27 (46%)	20 (34%)
18	13	2	10	43	2 (3%)	35 (49%)	26 (60%)	11 (26%)
3	2	0	3	7	0 (0%)	3 (23%)	4 (67%)	2 (33%)
19	12	3	13	126	1 (1%)	32 (42%)**	44 (32%)	15 (11%)
64 (18.2%)	43 (12.3%)	10 (2.8%)	42 (12.0%)	248 (70.5%)	5 (1.4%)	137 (51.9%)	101 (41.1%)	48 (19.5%)
349 (11.1%)	274 (8.7%)	117 (3.7%)	210 (6.7%)	1937 (61.8%)	54 (1.7%)	1184 (38.9%)	1010 (49.1%)	398 (19.3%)
						2271 (31.7%)	2812 (43.6%)	1062 (16.5%)

(Renal function: eGFR or serum creatinine; Albuminuria: albumin creatinine ratio or urine albumin). eGFR in ml/min/1.73m^2. * the percentages show the achieved blood pressure targets divided by the number of blood pressure measurements.** Percentage calculated with patients with eGFR < 60 ml/min/1.73m^2 as denominator (n = 77).

Table 3 Patient characteristics based on data from 2008 – 2011

Patient characteristic	Groups			
	Overall (*n*=8845)	Primary care (*n*=5709)	Consultation (*n*=2784)	Referral (*n*=352)
Demographics (SD)				
Age in years	71.4 (11.9)	73.6 (10.2)	66.7 (13.3)	72.0 (14.5)
Male sex	40.1%	42.7%	33.6%	48.3%
Co morbidity				
Diabetes	32.9%	35.9%	24.5%	51.4%
Hypertension	56.2%	57.8%	53.5%	52.0%
Cardiovascular disease	35.6%	36.2%	32.4%	52.8%
Laboratory (SD) [n]				
Creatinine in µmol/l	104.5 (28.0) [*n*=8843]	95.6 (18.5) [*n*=5708]	117.4 (23.7) [*n*=2783]	145.5 (73.5) [*n*=352]
eGFR in ml/ min/1.73m^2	56.4 (18.8) [*n*=8845]	61.3 (20.1) [*n*=5709]	47.1 (8.8) [*n*=2784]	41.3 (16.1) [*n*=352]
Fasting glucose in mmol/l	6.5 (1.8) [*n*=6968]	6.6 (1.9) [*n*=4688]	6.2 (1.6) [*n*=2001]	7.1 (2.3) [*n*=279]
Hemoglobin in g/dl			13.50 (1.55) [*n*=2087]	12.73 (1.91) [*n*=270]
Calcium in mmol/l			2.33 (0.13) [*n*=446]	2.31 (0.13) [*n*=89]
Phosphate in mmol/l			1.02 (0.19) [*n*=342]	1.13 (0.20) [*n*=59]
PTH in pmol/l			7.58 (5.02) [*n*=139]	11.74 (7.65) [*n*=17]
Albumin in g/l			38.8 (4.5) [*n*=272]	37.7 (5.8) [*n*=73]
Potassium in mmol/l			4.3 (0.45) [*n*=2241]	4.4 (0.58) [*n*=316]
Urine [(first and third quartile) n]				
Albumin urine in mg/l	15.0 (3.4–51.0) [*n*=2930]	20.0 (5.0-53.0) [*n*=2048]	6.0 (2.9-18.0) [*n*=724]	210.6 (89.3–489.0) [*n*=158]
Albumin/creatinine ratio	2.5 (0.9-6.1) [*n*=5040]	3.2 (0.9-6.4) [*n*=3556]	0.9 (0.8-2.3) [*n*=1257]	37.7 (12.4-58.8) [*n*=227]
Physical examination [(SD) n]				
Diastolic blood pressure in mm Hg	78.6 (9.6) [*n*=7325]	78.4 (9.3) [*n*=4888]	78.9 (9.8) [*n*=2151]	78.8 (11.2) [*n*=286]
Systolic blood pressure in mm Hg	142.6 (17.6) [*n*=7324]	143.8 (17.2) [*n*=4888]	139.5 (17.4) [*n*=2150]	145.2 (21.7) [*n*=286]

Table 3 Continued

Patient characteristic	Groups			
	Overall (*n*=8845)	Primary care (*n*=5709)	Consultation (*n*=2784)	Referral (*n*=352)
Medication prescribed in 2010				
Renin angiotensin blockers	55.9%	56.4%	53.7%	65.9%
B-blockers	46.4%	46.5%	45.4%	54.0%
Diuretics	41.6%	40.7%	41.9%	52.3%
Calcium antagonist	21.7%	21.4%	20.6%	34.1%
Statins	47.0%	48.8%	42.6%	51.7%
Vitamin D	3.9%	2.2%	6.1%	14.8%
Erythropoietin	0.3%	0.1%	0.5%	2.3%
Blood glucose lowering drugs	25.1%	27.3%	18.5%	40.6%
Antithrombotics	46.7%	48.3%	42.0%	57.9%
NSAIDs	21.3%	21.1%	22.2%	16.8%

'primary care group': treatment in primary care. 'consultation group': consultation of a nephrologist without referral. 'referral group': referral to secondary care.

Data analysis

CKD stage prevalences were calculated using the size of the registered population aged 18 years and over as the denominator. We used descriptive statistics to assess adherence to process and outcome indicators within 15 months prior to data extraction on March 1, 2011 and to evaluate FPs' recognition of CKD. Because of the hierarchical structure of our study (patient nested within practice) the analyses were based on the multilevel logistic regression model (PROC GLIMMIX in SAS). In this model both fixed and random effects can be analyzed. We performed a model with a random intercept and all other variables were fixed. This model was used to identify patient and practice characteristics associated with high quality care. The type of General Practice Information System was considered as a confounder, since differences between the systems could affect the quality of recording of both the independent variables and the outcomes. We started with a full model including all independent variables and excluded statistically non-significant variables one by one in a backward procedure. We considered a *P*-value <0.05 statistically significant. Descriptive analysis was conducted using SPSS version 20.0 (IBM PASW statistics 20) and multilevel logistic regression analysis was conducted using SAS V9.2.

Ethical approval

Ethical approval was not required according to the accredited Medical Research Ethics Committee Arnhem/Nijmegen registration number 2010/187.

RESULTS

Practice population

The 47 participating practices served a population of 207,469 people of whom 162,562 were over 18 years of age. Data on renal function (n=60,143) or albuminuria (n=19,359) were present for 64,102 patients (31%). More data were available for elderly: 71% of the population over 65 years of age had a renal function assessment. Diabetes was recorded in 10,623 patients (6.5% of the population), hypertension in 23,647 (14.5%) patients, and cardiovascular disease in 12,938 (8.0%) patients.

Study population

9295 patients met the criteria for CKD, resulting in a known prevalence of CKD in our study of 5.7%. K\DOQI stages 1–2 accounted for 1.05% (n=1712) and stages 3–5 for 4.66% (n=7583). 450 patients did receive secondary renal care and were not further analyzed. Of note, 91.8% of these patients fulfilled the criteria for referral. In the cohort of 8845 CKD patients treated by their FP, the guideline recommended treatment in primary care in 64.5%, consultation of a nephrologist in 31.5% and referral in 4.0% of the patients. Table 3 provides detailed characteristics.

Process and outcome indicators

FPs completely followed the guideline in 43% of their CKD patients for monitoring disease progression and in 2% for monitoring metabolic parameters in the 15 preceding months. Blood pressure was below 140/90mmHg in 43.6% and below 130/80mmHg in 16.5% of patients in whom a blood pressure measurement was available (n=6452). When we consider all patients, the achievement of blood pressure targets amounted 31.8% and 12.0% respectively. FPs recognized CKD in 31.7% by correctly using ICPC code U99.01. Table 2 provides further details on achievement of quality indicators.

Associated patient and practice characteristics

In the multilevel logistic regression analysis, a history of diabetes (OR 12.00; 95% CI 10.66–13.52) or hypertension (OR 2.49; 95% CI 2.23–2.78), and male gender were associated with better monitoring of disease progression (Table 4a). A history of cardiovascular disease was negatively correlated with monitoring of disease progression, as was urban practice location. Cardiovascular disease, duo practices and vocational training practices were positively associated with monitoring of metabolic parameters

Table 4a Significant results of multilevel logistic regression model on the association between patient- and practice-characteristics and QoC

Variable	Monitoring disease progression				
	eGFR	albumin urine	fasting glucose	blood pressure	complete
Patient characteristics					
Age					
18 - 45	0.39 (0.29 - 0.54)	1.19 (0.86 - 1.65)	0.58 (0.42 - 0.81)	0.33 (0.24 - 0.46)	
45 - 60	0.58 (0.49 - 0.68)	1.22 (1.05 - 1.42)	1.00 (0.85 - 1.17)	0.62 (0.53 - 0.73)	
60 - 75	0.79 (0.69 - 0.90)	1.26 (1.13 - 1.40)	1.34 (1.19 - 1.50)	0.90 (0.80 - 1.02)	
>= 75 (reference)					
Male sex		1.26 (1.14 - 1.39)			1.26 (1.13 - 1.40)
Diabetes	3.42 (2.94 - 3.97)	9.38 (8.39 - 10.49)	11.61 (10.02 - 13.46)	5.08 (4.42 - 5.84)	12.00 (10.66 - 13.52)
Hypertension	1.91 (1.70 - 2.14)	2.14 (1.93 - 2.37)	2.69 (2.42 - 2.99)	4.22 (3.77 - 4.72)	2.49 (2.23 - 2.78)
Cardiovascular disease		0.80 (0.72 - 0.89)	0.82 (0.74 - 0.92)		0.79 (0.71 - 0.88)
Practice characteristics					
Practice type					
Solo					
Duo					
Group (reference)					
Vocational training practice					
Urban location		0.53 (0.35 - 0.82)		0.47 (0.26 - 0.84)	0.47 (0.27 - 0.84)

Results are shown as odds ratios with 95% confidence intervals in parenthesis.

(Table 4b). Younger age was negatively associated with monitoring of metabolic parameters. Factors associated with recognition of CKD were a history of cardiovascular disease, hypertension, female sex and age. Blood pressure outcome target <140/90mmHg was positively associated with a history of diabetes and cardiovascular disease, and had a negative correlation with age.

Table 4b Significant results of multilevel logistic regression model on the association between patient- and practice-characteristics and QoC

Variable	Monitoring metabolic parameters				
	hemoglobin	calcium	phosphate	PTH	serum albumin
Patient characteristics					
Age					
18 - 45	0.41 (0.27 - 0.62)	0.10 (0.02 - 0.39)	0.06 (0.01 - 0.47)		0.18 (0.04 - 0.72)
45 - 60	0.44 (0.36 - 0.54)	0.33 (0.24 -0.46)	0.32 (0.22 - 0.47)		0.32 (0.21 - 0.49)
60 – 75	0.47 (0.39 - 0.57)	0.55 (0.42 - 0.71)	0.61 (0.46 - 0.81)		0.55 (0.39 - 0.76)
>= 75 (reference)					
Male sex					
Diabetes	0.66 (0.55 - 0.78)				
Hypertension	0.72 (0.64 - 0.87)				
Cardiovascular disease	1.28 (1.08 - 1.52)				
Practice characteristics					
Practice type					
Solo					
Duo					
Group (reference)					
Vocational training practice					1.97 (1.25 - 3.10)
Urban location					

Results are shown as odds ratios with 95% confidence intervals in parenthesis. PTH and complete monitoring of metabolic parameters yielded too few results for the model to work.

			Recognition	Outcome variables	
	potassium	complete		< 140/90 mmHg	< 130/80 mmHg
	0.22 (0.13 - 0.35)		0.27 (0.17 - 0.44)	1.72 (1.14 - 2.58)	
	0.50 (0.41 - 0.63)		0.39 (0.32 - 0.47)	2.03 (1.72 - 2.40)	
	0.65 (0.53 - 0.80)		0.68 (0.61 - 0.77)	1.32 (1.18 - 1.47)	
			0.86 (0.78 - 0.96)		
	1.64 (1.36 - 1.98)			1.15 (1.04 - 1.28)	1.18 (1.02 - 1.35)
	2.72 (2.31 - 3.19)		1.43 (1.28 - 1.60)		0.50 (0.43 - 0.57)
	1.47 (1.23 - 1.77		1.54 (1.38 - 1.72)	1.41 (1.27 - 1.57)	1.69 (1.47 - 1.93)
	0.91 (0.51 - 1.62)				
	1.64 (1.11 - 2.42)				

DISCUSSION

Our results show important gaps in the QoC in all aspects of CKD management. Monitoring of disease progression (43%), monitoring of metabolic parameters (2%), and CKD recognition (32%) were suboptimal. Most clinical relevance lies in the achievement of blood pressure targets (44% <140/90mmHg), for which there was evident room for improvement. History of diabetes was strongly associated with high QoC.

Recorded and expected prevalence and recognition

In the Netherlands, the estimated community prevalence of CKD is 10.4%, with 5.1% in CKD stages 1-2, and 5.3% in stages 3-5.(36) For our data, this implies that 21% and 88% of expected patients with K/DOQI stages 1-2 and 3-5 respectively could have been ascertained in primary care. Recorded CKD recognition was lower and amounted to 31.7% of potentially identifiable patients. Recognition is important, as it is associated with better quality of care.(37, 38)

In CKD stages 1 and 2 we found a high QoC for monitoring of disease progression. We hypothesize that the high prevalence of diabetes in these patients (62%), and thus their enrolment in the disease management program for diabetes, is the key reason for their renal function and albuminuria assessments.(39) This suggests that embedding of CKD care in a disease management program, comparable to that for diabetes, could yield better QoC. Another contributing factor is that the Dutch diabetes guideline advises annual monitoring of renal function.(40)

Strengths and limitations

A key strength of our study is the utilization of routine family practice data, which provides a realistic view on current gaps in care. Our study represents a large proportion of the (potential) CKD population in primary care, as data on renal function were available for most patients over 65 years of age. To accurately report on the QoC in routine family practice, we focused on patients under care of their FP and excluded patients under secondary renal care. To our knowledge, this is the only study that incorporated all CKD stages and factored in the association of practice characteristics.

Several limitations should be considered. We applied the guideline classification based on single creatinine and albuminuria assessments whereas at least two and three measurements are advised.(41) This might have led to a less accurate classification of patients but the approach is in line with most other CKD studies. Quality of care might be underestimated due to analysis of data routinely recorded in

the electronic medical record. It is not unlikely that care was provided, but was not or incompletely registered. Furthermore, FPs had little time to implement the guideline within our studied timeframe (January 1,2010 to March 1,2011) considering the guideline's introduction in November 2009.

Comparison with prior knowledge

Our results on monitoring of disease progression are in line with previous studies. An American study found a comparable annual eGFR assessment rate (86%), and a slightly lower albuminuria testing rate (30%).(25) Their research was conducted within multi-specialty group practices, housing both FPs and nephrologists, and included patients with CKD stages 3-4. Also, impressive results are shown in primary care CKD management in the United Kingdom, where they recorded an 82% albuminuria testing rate in CKD stages 3-5.(5) This may be because in the UK a pay for performance system is in place for managing chronic diseases in primary care: the Quality and Outcomes Framework (QOF).(42) In the Netherlands, FPs are not given incentives to manage CKD, but for diabetes local financial incentives for optimal diabetes care exist.(43)

Outcomes on metabolic parameter monitoring were low in our study compared to others. The earlier mentioned American study reported two to threefold better monitoring of hemoglobin, calcium and PTH,(25) as did another study on phosphate and PTH monitoring in stages 3b-4 in a university based, outpatient primary care clinic.(27) The presence of nephrologists close to the FPs, and the academic setting respectively may account for these differences.

The overall level of CKD recognition is not exceptional in our study, as other studies report electronic documentation of CKD between 4-38%.(25, 26, 37, 44-48) However, results from the Quality and Outcomes Framework show that important improvements are possible, as their recorded recognition amounted to 72%.(42, 49, 50) Another factor that may contribute to suboptimal levels of CKD recognition is hesitation among FPs to identify and code early stage CKD. Interviews reveal professional concern about creating patient anxiety, particularly in older people and those with CKD stage 3A, in whom clinical benefit was deemed less certain.(51)

Blood pressure targets were equally met in most other studies, as Italian research reports blood pressures <140/90mmHg in 45% of CKD patients; others report blood pressures <130/80mmHg between 13% and 54% depending on the included CKD stages.(37, 38, 52) The Quality and Outcomes Framework shows strong results with blood pressures <140/85mmHg in 72% of the CKD population.(5)

Previous research shows that patient factors associated with high quality of care are concurrent diabetes, hypertension or coronary artery disease, age >75 years, and male sex.(25, 38, 46, 53) Patient factors associated with low QoC are female sex, being uninsured, and black race.(25) Our findings are in line with these previous findings, except that cardiovascular disease was negatively associated with monitoring of disease progression. Possibly, monitoring of these patients was left at the discretion of a cardiologist.

Results derived from the Quality and Outcomes Framework in the UK show that vocational training practices, group practices and practices in less socially deprived areas were associated with a higher quality of care in general.(54, 55) We found a positive correlation between rural practice location and monitoring of disease progression, and between vocational training practice and monitoring of serum albumin.

Implications for practice and future research

The results of our study bring to light gaps in the quality of care in all aspects of CKD management, of which gaps in monitoring of albuminuria and metabolic parameters were most apparent. Of highest clinical relevance is the lack of reaching blood pressure targets and the lack of recognition. Comorbidity of diabetes appeared to be related with higher quality of care. This may well be because diabetes patients were treated in disease management programs. Possibilities to improve primary care CKD management could include the embedding of CKD care into a disease management program, comparable to diabetes.(56) This should not be a new single issue program, but should preferably be integrated in existing diabetes or cardiovascular programs to prevent fragmentation within primary care.(57) Feedback on laboratory results and FP education to increase CKD recognition can assist FPs to better identify CKD patients and subsequently provide a higher QoC.(37) Periodic reviewing of electronic medical records, with or without the support of nephrologists, could be a component of the disease management programs.(58) Introduction of a pay for performance system for CKD management has shown favorable results in the United Kingdom.(42)

Female sex was associated with lower quality of care. This may be a reflection of the fact that the MDRD formula leads to an overrepresentation of CKD in females, and possibly FPs are aware of this.(59) The introduction of the CKD-EPI formula will partly correct this, but will need implementation in primary care to make FPs aware of that effect.(60)

This study uncovered significant gaps in QoC in CKD management. Quality improvement strategies should focus on better recognition, systematic monitoring of disease progression including albuminuria, and focus on blood pressure targets.

Acknowledgements
The Dutch Kidney Foundation funded the study
Amgen provided a non-conditional grant
Participating practices
Lea Peters, research assistant
Reinier Akkermans, statistician

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Appendix

Table 1 CKD management recommendations provided by the interdisciplinary CKD-guideline for primary care and nephrology

	Annual monitoring of disease progression			
	eGFR	**albumin urine**	**fasting glucose**	**blood pressure**
Patients ≥ 65 years				
eGFR ≥ 60 and microalbuminuria	•	•	•	•
eGFR 45 – 60 and normo- or micro-albuminuria	•	•	•	•
eGFR 30 – 45 and normo- or micro-albuminuria	•	•	•	•
eGFR < 30 and normo- or micro-albuminuria	•	•	•	•
eGFR any and macroalbuminuria	•	•	•	•
Patients < 65 years				
eGFR ≥ 60 and microalbuminuria	•	•	•	•
eGFR 45 – 60 and normo- or micro-albuminuria	•	•	•	•
eGFR 30 – 45 and normo- or micro-albuminuria	•	•	•	•
eGFR < 30 and normo- or micro-albuminuria	•	•	•	•
eGFR any and macroalbuminuria	•	•	•	•

'primary care group': treatment in primary care. 'consultation group': consultation of a nephrologist without referral. 'referral group': referral to secondary care. eGFR in ml/min/1.73m^2

	Annual monitoring of metabolic parameters					
	hemoglobin	calcium	phosphate	PTH	serum albumin	potassium
	•	•	•	•	•	•
	•	•	•	•	•	•
	•	•	•	•	•	•
	•	•	•	•	•	•
	•	•	•	•	•	•
	•	•	•	•	•	•
	•	•	•	•	•	•

Appendix

Table 2 Practice characteristics

Practice type	N
Solo practice	6
Duo practice	16
Group practice	25
Vocational training practice	30
Rural location	15
General Practice Information System	
Medicom	25
Micro-HIS	6
MIRA	6
Promedico ASP	8
Promedico VDF	2

Appendix

Table 3a Classification of included CDK patients with diabetes under care of their GP using the interdisciplinary CKD-guideline for primary care and nephrology

	Albuminuria			
	Not known	Normal	Microalbuminuria	Macroalbuminuria
Patients ≥ 65 years (n = 2.179)				
eGFR ≥ 60			559	44
eGFR 45 – 60	149	673	253	30
eGFR 30 – 45	92	198	127	14
eGFR < 30	13	11	12	4
Patients < 65 years (n = 735)				
eGFR ≥ 60			418	20
eGFR 45 – 60	55	177	32	9
eGFR 30 – 45	6	8	5	2
eGFR < 30	3	0	0	0

Classification of patients based on renal function, albuminuria and age. 'primary care group': treatment in primary care. 'consultation group': consultation of a nephrologist without referral. 'referral group': referral to secondary care. eGFR in ml/min/1.73m^2

Appendix

Table 3b Classification of included CKD patients without diabetes under care of their GP using the interdisciplinary CKD-guideline for primary care and nephrology

	Albuminuria			
	Not known	Normal	Microalbuminuria	Macroalbuminuria
Patients ≥ 65 years (*n* = 4.297)				
eGFR ≥ 60			333	8
eGFR 45 – 60	1983	908	158	10
eGFR 30 – 45	540	216	64	9
eGFR < 30	57	6	3	2
Patients < 65 years (*n* = 1.634)				
eGFR ≥ 60			275	9
eGFR 45 – 60	833	413	37	3
eGFR 30 – 45	38	12	3	0
eGFR < 30	8	1	1	1

Classification of patients based on renal function, albuminuria and age. 'primary care group': treatment in primary care. 'consultation group': consultation of a nephrologist without referral. 'referral group': referral to secondary care. eGFR in ml/min/1.73m²

Appendix

Table 4a Performance on process- and outcome indicators for CKD patients with diabetes, within 15 months prior to data extraction

Patient group	N	Monitoring of disease progression					Monitoring of
		renal function	albu-minuria	Fasting glucose	blood pressure	complete	hemo-globin
Primary care group							
Age ≥ 65 eGFR ≥ 60 and micro-albuminuria	559	526	499	539	520	473 (85%)	
Age < 65 eGFR ≥ 60 and micro-albuminuria	418	369	349	386	349	314 (75%)	
Age ≥ 65 eGFR 45 – 60	1075	1013	858	1001	972	820 (76%)	
Total primary care	2052	1908 (93.0%)	1706 83.1%)	1926 (93.9%)	1841 (89.7%)	1607 (78.3%)	
Consultation group							
Age ≥ 65 eGFR 30 – 44	417	376	278	350	348	273 (65%)	212
Age < 65 eGFR 45 – 60	264	230	190	218	211	174 (66%)	77
Total consultation	681	606 (89.0%)	468 (68.7%)	568 (83.4%)	559 (82.1%)	447 (65.7%)	289 (42.4%)
Referral group							
Age ≥ 65 eGFR < 30	36	32	18	28	25	16 (44%)	23
Age < 65 eGFR 30 – 44	19	16	13	15	15	13 (68%)	11
Age < 65 eGFR < 30	3	2	0	1	2	0 (0%)	1
Macro-albuminuria	123	113	95	116	109	88 (72%)	48
Total referral	181	163 (90.1%)	126 (69.6%)	160 (88.4%)	151 (83.4%)	117 (64.6%)	83 (45.9%)
Total consultation and referral	862	769 (89.2%)	594 (68.9%)	728 (84.5%)	710 (82.4%)	564 (65.4%)	372 (43.2%)
Total	2914	2677 (91.9%)	2300 (78.9%)	2654 (91.1%)	2551 (87.5%)	2171 (74.5%)	

Process- and outcome indicators are derived from the interdisciplinary CKD-guideline for primary care and nephrology. For each indicator, performance in the preceding 15 months is shown.

	metabolic complications						Recog-nition	Blood pressure targets*	
	calcium	phos-phate	PTH	serum albumin	potassium	complete		<140/90 mmHg	<130/80 mmHg
								192 (37%)	71 (14%)
								166 (48%)	55 (16%)
							334 (31%)	448 (46%)	200 (21%)
								806 (43.8%)	326 (17.7%)
	63	52	25	43	312	19 (5%)	259 (62%)	191 (55%)	89 (26%)
	15	11	3	8	175	2 (1%)	59 (22%)	104 (49%)	37 (18%)
	78 (11.5%)	63 (9.3%)	28 (4.1%)	51 (7.5%)	487 (71.5%)	21 (3.1%)	318 (46.7%)	295 (52.8%)	126 (22.5%)
	8	4	3	4	28	1 (3%)	29 (81%)	10 (40%)	8 (32%)
	7	6	1	3	16	1 (5%)	11 (58%)	8 (53%)	5 (33%)
	0	0	0	0	1	0 (0%)	1 (33%)	0 (0%)	0 (0%)
	13	7	3	8	97	1 (1%)	19** (35%)	36 (33%)	15 (14%)
	28 (15.5%)	17 (9.4%)	7 (3.9%)	15 (8.3%)	142 (78.5%)	3 (1.7%)	60 (53.1%)	54 (35.8%)	28 (18.5%)
	106 (12.3%)	80 (9.3%)	35 (4.1%)	66 (7.7%)	629 (73.0%)	24 (2.8%)	378 (47.6%)	349 (49.2%)	154 (21.7%)
							752 (40.2%)	1155 (45.3%)	480 (18.8%)

(Renal function: eGFR or serum creatinine; Albuminuria: albumin creatinine ratio or urine albumin). * the percentages show the achieved blood pressure targets divided by the number of blood pressure measurements. ** Percentage calculated with patients with eGFR < 60 ml/min/1.73m^2 as denominator (n = 55).

Appendix

Table 4b Performance on process- and outcome indicators for CKD patients without diabetes, within 15 months prior to data extraction

Patient group	N	Monitoring of disease progression					Monitoring of
		renal function	albu-minuria	Fasting glucose	blood pressure	complete	hemo-globin
Primary care group							
Age ≥ 65 eGFR ≥ 60 and micro-albuminuria	333	302	264	273	290	224 (67%)	
Age < 65 eGFR ≥ 60 and micro-albuminuria	275	224	207	198	196	153 (56%)	
Age ≥ 65 eGFR 45 – 60	3049	2403	841	1623	2068	751 (25%)	
Total primary care	3657	2929 (80.1%)	1312 (35.9%)	2094 (57.3%)	2554 (69.8%)	1128 (30.8%)	
Consultation group							
Age ≥ 65 eGFR 30 – 44	820	657	211	354	545	179 (22%)	487
Age < 65 eGFR 45 – 60	1283	896	351	630	707	283 (22%)	546
Total consultation	2103	1553 (73.8%)	562 (26.7%)	984 (46.8%)	1252 (59.5%)	462 (22.0%)	1033 (49.1%)
Referral group							
Age ≥ 65 eGFR < 30	66	53	6	20	34	5 (8%)	50
Age < 65 eGFR 30 – 44	53	37	5	24	28	5 (9%)	29
Age < 65 eGFR < 30	10	8	0	3	4	0 (0%)	8
Macro-albuminuria	42	32	26	29	29	20 (48%)	20
Total referral	171	130 (76.0%)	37 (21.6%)	76 (44.4%)	95 (55.6%)	30 (17.5%)	107 (62.6%)
Total consultation and referral	2274	1683 (74.0%)	599 (26.3%)	1060 (46.6%)	1347 (59.2%)	492 (21.6%)	1140 (50.1%)
Total	5931	4612 (77.8%)	1911 (32.2%)	3154 (53.2%)	3901 (65.8%)	1620 (27.3%)	

Process- and outcome indicators are derived from the interdisciplinary CKD-guideline for primary care and nephrology. For each indicator, performance in the preceding 15 months is shown.

metabolic complications						Recog-nition	Blood pressure targets*	
calcium	phos-phate	PTH	serum albumin	potassium	complete		<140/90 mmHg	<130/80 mmHg
							87 (30%)	23 (8%)
							93 (47%)	30 (15%)
						753 (25%)	816 (39%)	285 (14%)
							996 (39.0%)	338 (13.2%)
129	106	50	78	564	33 (4%)	463 (56%)	243 (45%)	110 (20%)
78	62	29	39	638	17 (1%)	266 (21%)	371 (52%)	114 (16%)
207 (9.8%)	168 (8.0%)	79 (3.8%)	117 (5.6%)	1202 (57.2%)	50 (2.4%)	729 (34.7%)	614 (49.0%)	224 (17.9%)
16	12	2	12	44	1 (2%)	38 (58%)	17 (50%)	12 (35%)
11	7	1	7	27	1 (2%)	24 (45%)	18 (64%)	6 (21%)
3	2	0	3	6	0 (0%)	2 (20%)	4 (100%)	2 (50%)
6	5	0	5	29	0 (0%)	13** (59%)	8 (28%)	0 (0%)
36 (21.1%)	26 (15.2%)	3 (1.8%)	27 (15.8%)	106 (62.0%)	2 (1.2%)	77 (51.0%)	47 (49.5%)	20 (21.1%)
243 (10.7%)	194 (8.5%)	82 (3.6%)	144 (6.3%)	1308 (57.5%)	52 (2.3%)	806 (35.8%)	661 (49.1%)	244 (18.1%)
						1576 (29.7%)	1657 (42.5%)	582 (14.9%)

(Renal function: eGFR or serum creatinine; Albuminuria: albumin creatinine ratio or urine albumin). * the percentages show the achieved blood pressure targets divided by the number of blood pressure measurements. ** Percentage calculated with patients with eGFR < 60 ml/min/1.73m² as denominator (n = 22).

3

Disturbance of mineral metabolism in primary care CKD patients; an observational study

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ABSTRACT

Background In chronic kidney disease (CKD), abnormalities of mineral metabolism can occur early in the disease process. Changes in calcium and phosphate homeostasis and secondary hyperparathyroidism are metabolic complications of CKD that impact cardiovascular health and bone turnover. Data on disturbances of mineral metabolism in CKD in primary care are limited.

Aim To evaluate and find predictors of abnormalities in mineral metabolism in patients with CKD in primary care.

Design and Setting Cross sectional study in nine primary care practices in the Netherlands

Methods In patients with an eGFR $<$ 60 ml/min/1.73 m^2, identified during their evaluation for hypertension or diabetes mellitus, the prevalence of abnormal values of parathyroid hormone (PTH), calcium and phosphate was determined. Predictors of abnormal PTH levels were assessed.

Results A total number of 174 patients in primary care were investigated. Mean eGFR was 50.3 ml/min/1.73 m^2. An increase in PTH level above normal occurred in 40% of these patients with early stage of CKD in primary care. Although eGFR predicted abnormal PTH levels, its predictive value was low. Calcium and phosphate abnormalities were infrequent in this primary care population.

Conclusion PTH testing deserves attention in patients with CKD in primary care. Prospective studies should clarify whether PTH lowering affects cardiovascular prognosis of these patients. Awaiting this evidence, we suggest to follow the K-DOQI guideline that advises PTH testing in patients with CKD stage 3 or worse and to treat patients with elevated PTH levels with vitamin D.

HOW THIS FITS IN

Elevated PTH levels are related to cardiovascular morbidity and mortality, but data on mineral and bone metabolism in CKD patients under care of their general practitioner are scarce. PTH levels above normal were prevalent in 40% of patients with known chronic kidney disease in this primary care population. Since hyperparathyroidism is highly prevalent also in primary care, there is an urgent need to answer the question whether PTH-lowering will affect cardiovascular prognosis in this patient population. Awaiting this evidence, we suggest to follow the K-DOQI guideline that advises PTH testing in patients with CKD stage 3 or worse and to treat patients with persistent elevated PTH levels with vitamin D.

INTRODUCTION

Chronic kidney disease (CKD) is a highly prevalent condition especially in patients with diabetes or hypertension.(1) In primary care, the awareness of CKD in these patients has increased due to regular testing of serum creatinine and albuminuria in patients with diabetes or hypertension and due to reporting of estimated glomerular filtration rate (eGFR). (2, 3) CKD is not only a risk factor for end stage renal disease, but may also lead to complications, among which are cardiovascular morbidity and mortality. (4)

One of the complications of CKD is a change in calcium and phosphate homeostasis characterised by elevated serum intact parathyroid hormone (PTH) levels or abnormal values of calcium or phosphate. Abnormalities in these entities are considered part of the spectrum of CKD-Mineral and Bone disorder (CKD-MBD). A strong association has been established between PTH, calcium and phosphate abnormalities and increased risk of hypertension, CKD progression, adverse cardiovascular events, and mortality. (5, 6) This was also seen in CKD stage 3 and 4 where there was a significant increase in the prevalence of cardiovascular disease with increasing PTH levels.(7) Although controversy exists, prognosis of patients with secondary hyperparathyroidism can be improved by vitamin D treatment both in dialysis-patients and in non-dialysis-patients, which calls for early recognition of patients with CKD-MBD. (5, 8, 9)

International guidelines put emphasis on testing of metabolic disorders, but vary in defining the patients to be tested. The guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K-DOQI) and the KDIGO guidelines recommend that all patients with eGFR below 60 ml/min/1.73 m^2 undergo evaluation

for CKD-MBD by measuring PTH, calcium and phosphate.(10, 11) The NICE-guideline in the UK advices these measurements in patients with eGFR below 30 ml/min/1.73 m^2.(12) The Dutch interdisciplinary CKD-guideline advices evaluation in patients < 65 year with eGFR < 60 and in patients ≥ 65 year with eGFR < 45 ml/min/1.73m^2.(13) It is not clear which testing strategy is most effective in finding patients with elevated PTH.

Data on the prevalence of metabolic disorders in primary care patients are limited.

The few empirical data that are available, point to a limited uptake of MBD-assessment in primary care .(14, 15) Most data on metabolic disorders in CKD originate from patients referred to nephrologist care, indicating that PTH rises early in the course of CKD.(16-18) A better understanding of the actual prevalence and predictors of MBD in the CKD-population under care of general practitioners may enhance the uptake of testing in primary care.

The purpose of our cross sectional study was to evaluate the prevalence of disorders in PTH, calcium and phosphate in patients with CKD who are under control in primary care for their diabetes or hypertension. In addition, we analysed which factors predicted metabolic disorders in these patients.

METHOD

Study design

In this cross-sectional study we described and analysed the data of patients with CKD in a primary care setting. These data are part of a cluster randomised controlled trial in which the effectiveness of a shared care model between general practitioner (GP), nurse physician and nephrologist will be compared with usual care in patients with diabetes mellitus type 2 and/or hypertension with CKD.

We collected baseline data regarding demographic and clinical characteristics as mentioned in Table 3.

Participants

The study took place in nine general practices that are part of the Academic Practice-based Research Network of the Radboud University Nijmegen Medical Centre in 2008.(19) These practices have a total of 54.231 patients. From the electronic patient files we selected all adult patients with hypertension and/or diabetes mellitus type 2 who were under care of the GP for their diabetes or hypertension treatment.

Patient were eligible if the yearly measurement of eGFR was below 60 ml/min/1.73 m^2. The GPs could also include patients if eGFR below 60 ml/min/1.73 m^2 was newly found at the annual diabetes or hypertension control. Patients with serious medical or psychiatric conditions and patients under specialist care for CKD were excluded. Eligible patients were invited to take part in the study when they visited the practice for a regular consultation. In the patients who agreed to participate, eGFR was measured again and if the result was found to be below 60 ml/min/1.73 m^2 the patients were included in the study.

Laboratory measurements

Samples for PTH-analysis were put on ice immediately after blood sampling and analysed within two hours. If this was not possible, samples were centrifuged for 10 minutes at a minimum of 3000 rotations per minute and the serum was saved in a refrigerator until analysis. All clinical chemical analyses were performed by the Laboratory of Clinical Chemistry of the Canisius Wilhelmina Hospital in Nijmegen, the Netherlands. Creatinine, calcium, phosphate and PTH were measured on a routine chemistry analyzer (Roche Modular PE Analytics). PTH was measured with the Sandwich principle using an ECLIA technique (Elecsys PTH reagens, Roche). The normal value for PTH was $<$ 6.9 pmol/l. Serum creatinine was measured enzymatically. Calibration was traceable to isotope dilution mass spectrometry. The eGFR was calculated from the Modification of Diet in Renal disease (MDRD) equation: eGFR=175x (serum creatinine (μmol/l) x0.0113) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.210 if black).(20) Calcium levels were corrected for albumin levels.

Albuminuria was defined as an albumin/creatinineratio ≥ 2.5 mg/mmol in male or ≥ 3.5 mg/mmol in female patients. Blood pressure was measured three times after a five-minute rest with an oscillometric device. The mean of the two last measurements was used for the analysis.

Statistical analysis

Statistical differences between the variables were calculated by Student's t-tests for continuous outcomes and Chi-square tests for dichotomous outcomes using SAS version 9.2. For the application of the Student's t-test Pooled standard error or Satterthwaite approximation were chosen based on the F-test for variances. Stepwise logistic regression was used to determine risk factors for abnormal PTH-levels. For this model variables were selected with a univariate p-value $<$0.15.

We considered a p-value of less than 0.05 statistically significant.

RESULTS

Participants

4393 patients with diabetes and/or hypertension were under care of the GPs. Figure 1 gives an overview of the inclusion process. When comparing the included group to the non-included group of patients with an eGFR below 60 ml/min/1.73 m^2 no differences were found besides vitamin D treatment and heart failure (table 1). Relatively more male patients were included. Table 2. Shows the distribution of patients over CKD-stages.

PTH

In 11 patients a PTH-analysis could not be performed due to practical barriers. Mean PTH-level was 7.2 (SD 3.7) pmol/L. An elevated PTH level (PTH ≥ 6.9 pmol/L) was found in 40.5% of the patients (Table 3). Patients with an elevated PTH level had a significantly lower eGFR than those with a normal PTH level (difference 4.5 ml/min/1.73 m^2).

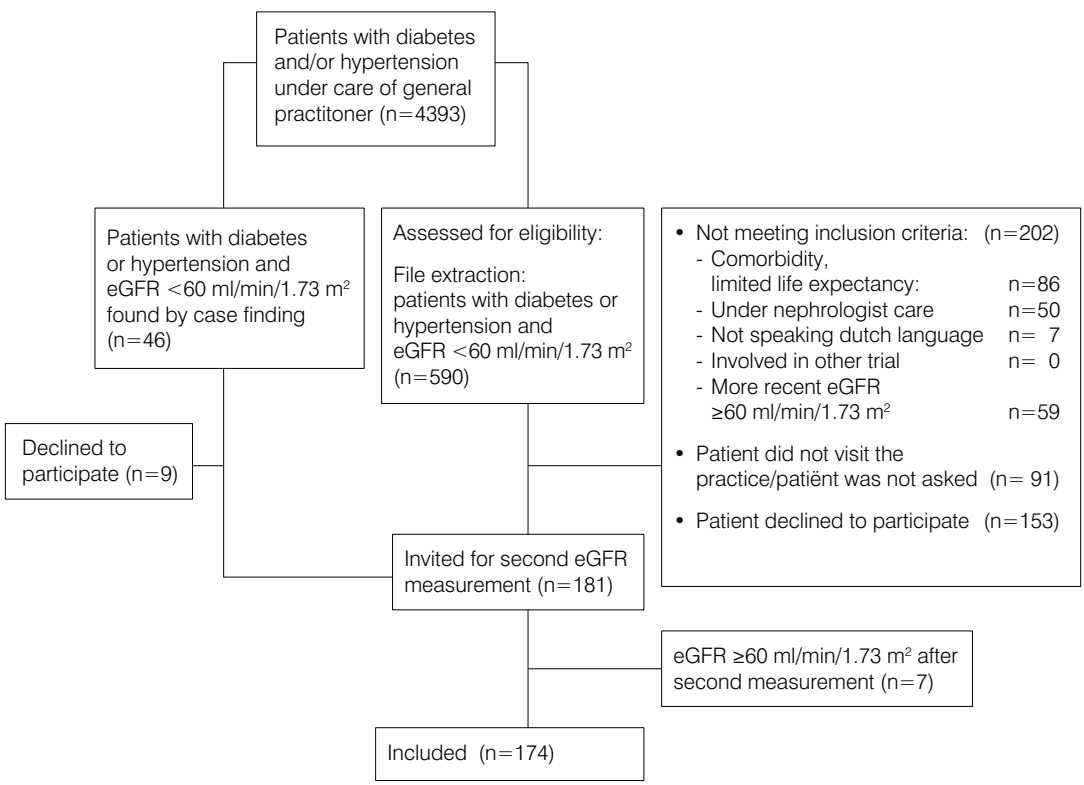

Figure 1 Inclusion process

Table 1 Differences between included and non-included patients with diabetes and hypertension and eGFR<60 ml/min/1.73 m² in 9 primary care practices

	Patients with MDRD<60 ml/min/1.73 m²			
	Not included in the study n = 448 (72%)	Included in this study n = 174 (28%)	Difference (95% CI)	P value *
Age in years (SD)	73.5 (10.2)	72.9 (8.1)	0.7 (-0.9 to 2.2)	0.39
Sex, male (%)	125 (28%)	77 (44%)		<0.001
Blood pressure Syst	146.0 (18.9)	143.5 (21.9)	2.5 (-1.3 to 6.2)	0.19
mmHg (SD) Diast	79.1 (10.1)	78.0 (13.5)	1.1 (-1.1 to 3.4)	0.31
Hypertension (no diabetes)	288 (64%)	109 (63%)		0.70
Diabetes, (normo- and hypertension)	160 (36%)	65 (37%)		0.70
eGFR ml/min/1.73m²	49.2 (9.5)	50.3 (7.0)	-1.1 (-2.5 to 0.3)	0.11
Medication				
Vitamin D	23 (5%)	2 (1%)		0.02
Thiazides	46 (10%)	23 (13%)		0.29
Bifosfanates	12 (3%)	1 (0.6%)		0.12 **
Iron supplements	13 (3%)	3 (2%)		0.58**
Agents acting on the renin-angiotensin system	284 (64%)	123 (71%)		0.09
Cardiovascular Comorbidity				
Myocardial infarction	48 (11%)	19 (11%)		0.94
Heart failure	53 (12%)	9 (5%)		0.01
TIA	32 (7%)	13 (7%)		0.89
CVA	62 (14%)	16 (9%)		0.12
Peripheral arterial disease	37 (8%)	20 (11%)		0.21

* T-test and Chi-square test for continuous and dichotomous outcomes **Fisher's exact test

Table 2 Distribution of patients over CKD-stages and prevalence of PTH-levels in these stages

	Number (%), n=174	Number PTH known	PTH <6.9 pmol/l, n=97*	PTH ≥6.9 pmol/l, n=66*
Stage 3a	129 (74.1%)	123	83 (67.5 %)	40 (32.5%)
eGFR 45-60 ml/min/1.73 m^2				
Stage 3b	40 (23.0%)	36	14 (38.9%)	22 (61.1%)
eGFR 30-45 ml/min/1.73 m^2				
Stage 4	5 (2.9 %)	4	0	4 (100%)
15-30 ml/min/1.73 m^2				
Stage 5	-		-	-
<15 ml/min/1.73 m^2				

*patients with missing PTH levels are excluded

Variables that entered the equation for stepwise logistic regression modelling were eGFR, triglycerides, heart failure and diuretics as factors predicting abnormal PTH, with p-values in univariate analysis of 0.0004, 0.0008, 0.06 and 0.07 respectively. For diuretics the odds ratio was 2.7 (95% confidence interval 0.9 to 7.9); for heart failure the odds ratio was 4.7 (95% confidence interval 0.9 to 24.3). Age, sex, myocardial infarction, body mass index, blood pressure, fasting glucose, HbA1c, haemoglobin, LDL-cholesterol, HDL-cholesterol, potassium and urine albumine-creatinine ratio did not enter the equation because p-values in univariate analysis were >0.15. By stepwise logistic regression eGFR and triglycerides were identified as predicting abnormal PTH-levels (chi-square statistic 0.0012 and 0.0017). The Receiver Operating Characteristic curve of eGFR predicting abnormal PTH was very flat and not of any help in defining eGFR cut-off values (appendix 1).

We additionally performed stepwise linear regression to assess what factors contributed to the absolute level of PTH. eGFR, heart failure and triglycerides contributed (partial R-square 13.5%, 6.0% and 2.0% respectively). Use of diuretics showed multicollinearity with heart failure.

Other metabolic disturbances

All serum calcium levels were above 2.1 mmol/l. Three subjects showed a calcium level ≥ 2.54 mmol/l. None of the subjects had an elevated phosphate level.

Table 3 Characteristics of patients with elevated PTH levels

N=163				
	PTH <6.9 pmol/l,	**PTH ≥ 6.9 pmol/l**	**Difference**	**P value**
Number	97 (59.5%)	66 (40.5%)		
Age (years)(SD)	72.6 (8.1)	73.6 (8.1)	-0.9 (-3.5 to 1.6)	0.47
Sex ,male(%)	42 (43%)	32 (48%)		0.51
eGFR (ml/min/1.73 m^2)	51.3 (5.9)	46.7 (9.0)	4.5 (2.0 to 7.0)	<0.001
BMI	28.7 (4.9)	29.1 (4.4)	-0.4 (-1.9 to 1.0)	0.56
Diabetes	38 (39.2%)	24 (36.4%)		0.72
Albuminuria : (n, %)	17 (18%)	18 (29%)		0.12
n=157				
Hb (mmol/l)	8.8 (0.9)	9.0 (0.8)	-0.2 (-0.5 to 0.1)	0.22
Calcium (mmol/l)	2.35 (0.1)	2.34 (0.1)	0.00 (-0.03 to 0.04)	0.88
Phosphate (mmol/l)	1.11 (0.18)	1.08 (0.17)	0.03 (-0.02 to 0.09)	0.24
HbA1c (%) in patients with diabetes	6.9 (0.84)	7.5 (1.16)	-0.56 (-1.1 to -0.05)	0.03
LDL (mmol/l)	2.88 (0.99)	2.68 (1.1)	0.2 (-0.12 to 0.53)	0.22
HDL (mmol/l)	1.35 (0.37)	1.35 (0.52)	-0.006 (-0.15 to 0.14)	0.93
Triglyceride (mmol/l)	1.57 (0.62)	2.01 (0.90)	-0.44 (-0.70 to -0.19)	0.007
Medication:				
Calcium	0	0		
Thiazides	10 (10.3%)	11 (16.7%)		0.23
Loop diuretics	6(6.2%)	10 (15.2%)		0.06
Drugs affecting bone structure	0	1 (1.5%)		0.22
Cardiovascular co-morbidity				
Myocardial infarction	11 (11%)	6 (9%)		0.64
Heart failure	2 (2%)	6 (9%)		0.04
TIA	7 (7%)	6 (9%)		0.66
CVA	8 (8%)	7 (11%)		0.61
Peripheral arterial disease	9 (9%)	7 (11%)		0.78

* T-test and Chi-square test for continuous and dichotomous outcomes

DISCUSSION

In this observational study in primary care we found that serum PTH levels rose early in the disease process. Increased PTH values occurred in 40 % of the patients with eGFR below 60 ml/min/1.73 m^2. In contrast, abnormal values of calcium and phosphorus were rare.

Strengths and limitations

This study made use of carefully defined diagnosis and laboratory results. The diagnosis of CKD was based on two evaluations of eGFR three or more months apart, whereas other studies in the general population only use one eGFR measurement on which to base diagnosis. One single laboratory performed the measurements and measurements were well-standardised. Furthermore we paid close attention to the pre-analytical handling of PTH samples. The laboratory assessment was performed within a few hours after sampling or blood was saved on ice.(21) The study size is relatively small, but large enough to explore quality and quantity of metabolic disturbances in a group of CKD patients that is daily seen in primary care.

We should consider some limitations of this study. First, our research was based on patients with diabetes or hypertension. We chose to focus on this group since the majority of patients under care for CKD in general practice will have diabetes or hypertension. (11, 22) Second, the protocol of the Sharing study- that asked patients to come four times to the practice- may have caused a selection of patients. Table 1 however reveals that the included patients did not differ from the non-included patients with respect to co-morbidity. If there has been a selection, it would have been the relatively vital patients that were included. For interpretation of the results this would mean that prevalence of metabolic abnormalities is more likely to be higher lower than the results we found. Third, the K-DOQI guideline advises yearly measurement of serum bicarbonate to detect metabolic acidosis in patients with CKD. Bicarbonate measurement however was not possible yet in our primary care setting. Bicarbonate disorders are mainly observed in patients with eGFR $<$ 30 ml/min/1.73 m^2.(23) As 97% of our study population had an eGFR$\geq$30 ml/min/1.73 m^2, we presume that metabolic acidosis will not play a major role in our study population.

Comparison with existing literature

We did not find other studies that evaluated the prevalence of disorders of mineral metabolism in known CKD patients in primary care only. The most comparable data derive from the prevalence of abnormalities in serum calcium, phosphate and PTH in a cross-sectional analysis of 1814 out-patient-clinic patients (71% primary care practices) with CKD stages 3–5 in North America.(24) Elevated PTH was present in

56% of patients with eGFR <60 ml/min/1.73m^2, which is higher than the 40.5 % we found. This can be explained by the fact that mean eGFR in the US study was 40 ml/min/1.73 m^2, clearly below the mean of 50 ml/min/1.73 m^2 in our study. A difference in race could also have been of influence; we will comment on that further in the discussion. In line with our data, calcium and phosphate values did not become abnormal until eGFR fell below 40 ml/min per 1.73m^2. In a community-based screening program -the Kidney Early Evaluation Program (KEEP)- and in epidemiological data from the National Health and Nutrition Examination Survey, Vasalotti et al found that as eGFR fell from 60 to 30 ml/min/1.73 m^2, calcium level decreased, phosphate level increased, and PTH level increased.(25) In summary, the evidence available points to a rise of PTH in early stages of CKD and our study confirms that this is the case in CKD patients with diabetes of hypertension in general practice.

Secondary hyperparathyroidism can be caused by a lack of renal activation of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitaminD3 but could -especially in elderly patients- as well be caused by a lack in inactive vitamin D. As laboratory results on vitamin D levels were not available, we cannot comment on that aspect.

Race may be of influence on secondary hyperparathyroidism. In blacks secondary hyperparathyroidism was more prevalent than in whites.(26) We were not informed on the race of patients in our study, but know that the population in the research practices is mainly (>95%) Caucasian.

Predicting factors

In our study, eGFR and triglycerides predicted abnormal PTH levels and heart failure contributed to the absolute PTH-height. The relation of elevated PTH with eGFR and heart failure is in line with findings in other studies. Cardiovascular disease, age, BMI ≥30, albuminuria and absence of diabetes were predicting factors in the community based study of Vassalotti et al. (25) De Boer et al. found in 218 outpatient nephrology patients that PTH was associated with eGFR and with a history of congestive heart failure and myocardial infarction.(27) The relation of triglycerides to elevated PTH was not found in other studies. In our study the overall contribution was very low and probably not of any clinical significance. Based on our results, we cannot define a PTH-testing strategy. Applications of the PTH-testing advices of the guidelines available (appendix 2) revealed that the K-DOQI and KDIGO guidelines best enable finding patients with secondary hyperparathyroidism.

Other metabolic disturbances

Further metabolic disturbances were found in a cross sectional study in veterans (>65 years) with mean eGFR of 47 ml/min/1.73m^2. 2.5% of participants had hyper-

kalemia and 4.4% had hyperphosphatemia. PTH was not tested.(28) Hyperphosphatemia was not found in our study. This could be due to the small number of patients tested and the fact that mean eGFR was relatively high.

Implications for research and practice

As PTH is related with adverse outcomes in CKD, and the prevalence of abnormal PTH in early stages of CKD is high, PTH-testing in primary care deserves more attention. The effectiveness of vitamin D in lowering PTH levels has been proved and the effects on prognosis were positive as well in dialysis as in non-dialysis patients. (5, 9, 29) The K-DOQI-guideline advises correction of MBD-abnormalities by native vitamin D amongst other therapies. In patients in whom serum PTH is rising and remains above the upper limit of normal for the assay despite correction of modifiable factors, treatment with calcitriol or vitamin D analogs is suggested by the KDIGO guideline.(11) However, convincing evidence that adverse cardiovascular outcome could be prevented or delayed by early detection and treatment of elevated PTH is not available yet.(8, 30) In primary care, PTH may prove to be a useful additive risk factor in identifying CKD patients who have a higher cardiovascular risk.

Given the frequency of elevated serum-PTH in a primary care population that comes forward in this study there is a need for further research on the effects of PTH lowering in primary care on cardiovascular morbidity and mortality. Awaiting this evidence, general practitioners may consider to check PTH-levels in patients with CKD stage 3 or worse and prescribe vitamin D in patients with elevated PTH levels.

Acknowledgements

Marjan Schoneveld and Wouter Koop of the laboratory of the Canisius Wilhelmina Hospital Nijmegen were very helpful in organising the laboratory tests.

We would like to thank the participating patients, the general practitioners and assistants of the NMP-practices.

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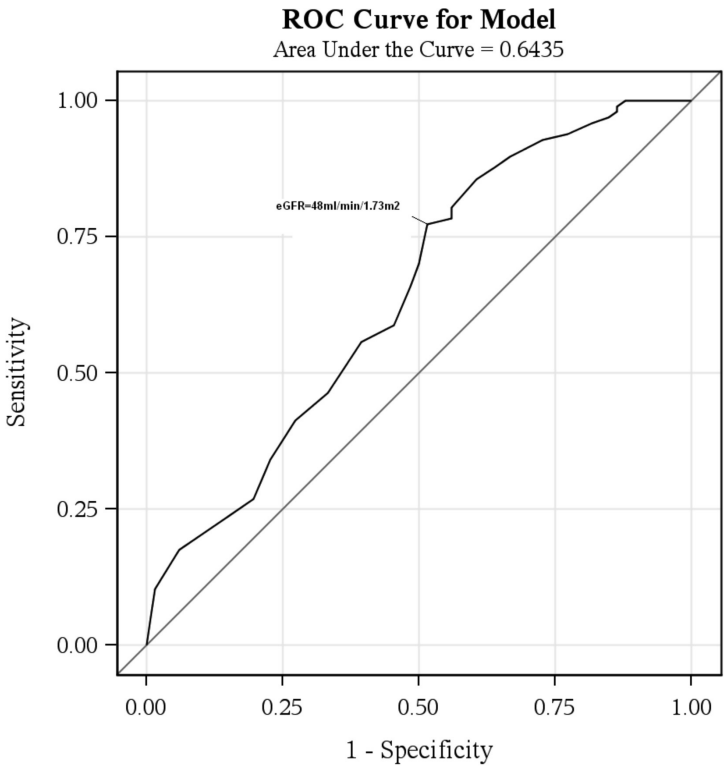

Appendix 1 Receiver Operating Characteristic curve of eGFR MDRD predicting PTH-levels

Appendix 2 Number and % of patients with increased PTH that would be found following the testing strategies of the K-DOQI guideline, the NICE guideline and the Dutch interdisciplinary CKD-guideline for primary care and nephrology

	K-DOQI: all patients with eGFR < 60 ml/min/1.73 m²	NICE: all patients with eGFR < 30 ml/min/1.73 m²	Dutch: patients<65 year AND eGFR<60 ml/min/1.73 m²; patients ≥65 year and eGFR <45 ml/min/1.73 m²
Number of patients with elevated PTH/number of patients tested	66/163 (40.5%)	4/4 (100%)	33/62 (53.2%)
% of elevated PTH diagnosed	66/66 (100%)	4/66 (6.1%)	33/66 (50%)
Mean PTH (pmol/l) in tested patients (SD)	7.2 (3.7)	12.5(3.1)	8.6 (4.7)
Range	0.9-22.9	11.0-17.1	0.9-22.9
Mean PTH (pmol/l) of non-tested patients (SD)	-	7.0 (3.6)	6.3 (2.5)
PTH-range of non-tested patients		0.9-22.9	2.8-15.0

4

Effect of shared care on blood pressure in Chronic Kidney Disease patients; a cluster randomised controlled trial

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In press *British Journal of General Practice*

ABSTRACT

Background: Chronic kidney disease (CKD) is highly prevalent in patients with diabetes or hypertension in primary care. A shared care model between general practitioner, nurse practitioner and nephrologist could improve quality of care in these patients.

Aim: to assess the effect of a shared care model in managing CKD-patients with diabetes or hypertension

Design: A cluster randomised controlled trial

Setting: Nine general practices in the Netherlands

Method: Five practices were allocated to the shared care model and four to usual care during one year. Primary outcome was the achievement of blood pressure(BP)-targets (130/80mmHg) and lowering of BP in patients with diabetes mellitus or hypertension and estimated Glomerular Filtration Rate(eGFR)<60ml/min/1.73 m^2. Secondary outcome measures: laboratory variables, use of lipid lowering drugs or renin-angiotensin system inhibitors, smoking and functional health status.

Results: 99 intervention and 75 control patients were included. Data of 90 intervention and 74 control patients could be analysed. BP after one year was 134.7/73.8mmHg in the intervention and 142.9/80.9mmHg in the control group (difference systolic:8.2 mmHg, 95%CI 3.6to12.9; diastolic:4.7mmHg, 95%CI 1.1to8.4). The proportion of patients that achieved systolic and diastolic BP-targets was 44%/71% in the intervention group versus 22%/50% in the control group. BP in the intervention group decreased with 8.1(95%CI 4.8to 11.3) /1.1(95%CI -1.0to3.2)mmHg compared to -0.2(95%CI -3.8to3.6)/-0.5(95%CI-2.9to1.8) mmHg in the control group. Use of lipid lowering drugs, angiotensine-system inhibitors and vitamin D was higher in the intervention group. Parathyroid hormone was lower in the intervention group. Other laboratory variables, functional health status and smoking did not differ.

Conclusion: A shared care model between general practitioner, nurse practitioner and nephrologist is beneficial in reducing BP in CKD-patients in primary care.

INTRODUCTION

The high and rising prevalence of Chronic Kidney Disease (CKD), amounting to 13% in the general population in the USA and 7% in primary care in the UK, places a burden on health care facilities.(1, 2) Among the risk factors contributing to CKD, diabetes and hypertension are the most common.(3) CKD can progress to end stage renal disease. The awareness of CKD is predominantly fostered by the recognition that CKD is an important risk predictor for coronary events and cardiovascular mortality.(4, 5) Timely intervention, directed at cardiovascular risk factors, can decrease the loss of renal function and the incidence of cardiovascular disease.(6-8) Guidelines provide recommendations for treatment of CKD.(9, 10) However, treatment targets are often not met.(11-13)

There is a significant evidence gap in how to best organise the care for CKD-patients.(14) A multidisciplinary approach has been proposed.(15) Shared care between primary and secondary care has been successful in other chronic conditions.(16) Observational studies on shared care for patients with CKD show promising results.(17) However, the effectiveness of shared care for CKD-patients has not yet been proved in randomised trials.(18)

We developed a shared care model for CKD-patients in primary care in which the nurse practitioner (NP) played a central role and a nephrologist and a nephrology nurse could be consulted. In a cluster randomised controlled trial we tested whether the model led to improved quality of care in patients with CKD and diabetes or hypertension. Lowering of blood pressure (BP) was the primary outcome.

METHOD

Setting

The study concerned nine general practices (54,231 patients) that are part of the Academic Practice-based Research Network of the Radboud University Nijmegen Medical Centre.(19) Usual care for diabetic and hypertensive patients in these practices is given in a structured setting with the help of NPs. Patients with diabetes or hypertension are seen every three months. Once a year an extensive control including renal function monitoring is performed according to the national evidence based practice guidelines.(20, 21) BP-measurements are performed according to a BP-measurement protocol, which requires a rest period and noting the mean of two BP-measurements.

We included adult patients (>18 years old) who were treated for hypertension or diabetes mellitus type 2 by their general practitioner(GP) and had an estimated glomerular filtration rate(eGFR) measurement<60ml/min/1.73 m^2(MDRD formula). We informed the GPs which patients lacked the annual information on renal function, so the GPs could have them tested and include them if an eGFR below 60 ml/min/1.73 m^2 was newly found. Exclusion criteria were serious medical or psychiatric conditions, drug or alcohol abuse, specialist CKD-care in the last year, inability to understand Dutch language (including cognitive disorders) and participation in another intervention trial. Eligible patients were invited to take part in the study when they visited the practice for a regular consultation until a minimum of 20 and a maximum of 28 patients per practice were included. Patients were included if they had given written informed consent and if a second eGFR-measurement was still below 60 ml/min/1.73 m^2.

Randomisation was carried out at the level of general practices because the intervention involved changes to the practice organisation. Practices were stratified by the mean BP of all eligible patients and then randomly allocated to intervention or control group. In the control practices patients were identified and included at the start of the study. To avoid bias by study inclusion, patients were asked to give written informed consent only at the time of the final measurement at the end of the trial, and their GPs and NPs were informed at that occasion.

To show a clinically relevant difference in the decline of BP of 5mmHg (standard deviation of BP difference 10mmHg, alpha=0.05 beta= 0.20 and intra-cluster correlation coefficient (ICC) 0.03) the study was powered to contain nine practices with 25 patients per practice.

Intervention

The multifaceted intervention consisted of training of professionals, structured care by NPs and the opportunity to ask advice from a nephrology team. In Spring 2008 NPs and GPs of intervention practices were trained by a nephrology team. BP-measurement and treatment, proteinuria, cholesterol lowering, blood glucose management and lifestyle advice were the main issues. A protocol, based on the K/DOQI guideline, was provided with treatment goals (Table 2) and treatment advice. (10) During the following intervention year, NPs received two extra training sessions on treatment of hyperparathyreoidism and anaemia. The NP saw patients every three months for a 20-minute consultation, in which BP-treatment was the main aim. Patient and NP decided together which other treatment goals were to be prioritised. GPs supervised the consultation afterwards. GPs and NPs could, if necessary, consult a nephrology team in a protected digital environment.(22)

Outcome

Reduction in BP was the primary outcome, defined as the difference between the usual BP- measurement at baseline and the study BP-measurement after one year. At the end of the trial, BP and the number of patients meeting the BP-target(130/80mmHg) were compared between control- and intervention group. Other quality of care variables were kidney disease measures (as mentioned in table 2) and the number of patients that reached the treatment goals. Additionally, functional status and use of angiotensin system inhibitors and lipid modifying agents were measured. The number of consultations with the nephrologist and the number of referrals were described.

At baseline, the NP collected data in the intervention group (as mentioned in table 2). After one year the same measurements were performed in patients in both intervention and control practices. Study BP was measured with an oscillometric device (Stabil-O-Graph). After a five-minute rest, three measurements were taken with the patient in a sitting position. The mean of the last two measurements was used for analysis. In patients with atrial fibrillation BP was measured manually with a sphygmanometer. The latest noted usual BP-measurement before inclusion was used as the baseline value for BP.

Clinical chemical analyses were performed by the laboratory of the Canisius Wilhelmina Hospital in Nijmegen, the Netherlands. Creatinine, calcium, phosphate and PTH were measured by a Roche Modular analyser. Blood samples for PTH analysis were put on ice immediately after blood sampling and analysed within two hours. If this was not possible, samples were centrifuged and saved in a refrigerator until analysis. Serum creatinine was measured enzymatically with calibration traceable to the international standard (IDMS) reference material. The eGFR was calculated from the MDRD-equation.(23) Calcium levels were corrected for albumin levels. Haemoglobin was measured on a Sysmex XE-2100 instrument. Albuminuria was defined as an albumin/creatinineratio ≥ 2.5 mg/mmol in male or ≥ 3.5 mg/mmol in female patients.

COOP Wonca Charts were used to obtain additional information about the patient's functional capacity.(24)

Statistical analysis

Descriptive analyses were used to describe the characteristics of the patients in both groups. Because of the hierarchical structure of the study (patient nested within practices) multilevel analyses were performed for between group and within group differences. These analyses took account of the variability associated with each level of nesting. A random intercept model with other variables fixed was used. For dichotomous

variables we performed a multilevel logistic model. BP comparison between intervention and control group was analysed by analysis of covariance with the follow up BP measurement as an outcome and the baseline BP measurement (last noted BP in the patient file) as a covariate.(25)

The ICC was calculated from pre-intervention BP-data from both intervention and control group.SAS® Proprietary Software 9·2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses and multilevel analyses were performed with PROC MIXED for continuous outcomes and PROC GLIMMIX for dichotomous variables.

RESULTS

Figure 1 shows a flow-chart of participating practices and patients. Five intervention practices included 16, 12, 20, 23 and 28 patients respectively. Four control practices included 6, 23, 19 and 27 patients. Nine patients from four practices in the intervention group did not finish the trial. Two of them died (of lung carcinoma and heart failure), three patients stopped because their general condition worsened, four because they did not want to come for extra control visits any more. One patient in the control group was excluded from the analysis because of extreme BP-values, that were considered as invalid measurements (270/170mmHg). Usual systolic BP at baseline did not differ between intervention and control group, whereas diastolic BP was lower in the intervention group (table 1).

BP after 1 year was lower in the intervention group than in the control group: systolic BP was 8.2(95%CI:3.6 to 12.9) mmHg lower, diastolic BP was 4.7(95%CI:1.1 to 8.4) mmHg lower. The number of patients that reached the treatment goal for systolic BP in the intervention group (44.4%) was higher than in the control group (21.6%)(OR 2.9 (95%CI 1.4 to 5.8; p=0.003). For diastolic BP these percentages were 71.1% and 50.0% respectively(OR 2.5; 95%CI 1.3 to 4.7; p=0.007)(table 2). The decrease in systolic BP in the intervention group was 8.1 (95% CI 4.8 to 11.3) mHg compared to -0.2(95% CI -3.8 to 3.6)mmHg in the control group (table 2). The decrease in diastolic BP did not differ between intervention and control group. The ICC was 0.11 for systolic BP and 0.15 for diastolic BP. Patients in the intervention group received more renin-angiotensin system inhibitors, lipid lowering drugs and vitamin D than patients in the control group. Laboratory values did not differ between intervention and control group, besides PTH, which was lower in the intervention group (table 2).

During the intervention cholesterol and LDL-levels decreased in the intervention group, parallel with an increase in the use of lipid lowering drugs (appendix 2).

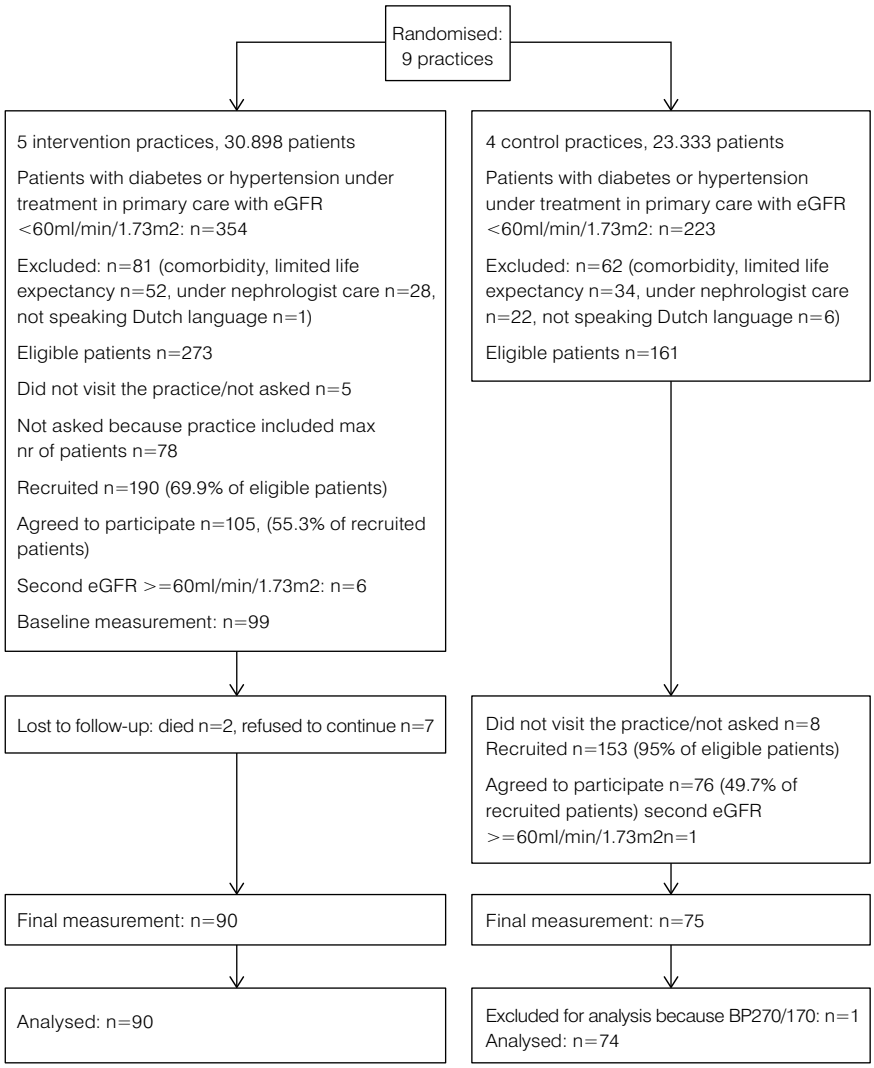

Figure 1 Flow chart of participating practices and patients

In 31 patients in the intervention group 50 consultations were performed between GP and nephrologist. None of these 50 consultations resulted in a referral. In the intervention group two patients were referred to a nephrologist. In the control group one patient was referred.

Table 1 Patient characteristics at baseline, derived from the electronic patient record

	Control group	Intervention group
Sex(N), male (%)	39 (52.7)	34 (37.8)
Age (year)	72.4 (8.2)	73.9 (8.0)
Creatinine (μmol/l)	117.6(21.2)	109.0(24.9)
eGFR (ml/min/1.73 m^2)	50.0 (6.7)	49.1(7.9)
Systolic usual office BP (mmHg)[1]	142.5(15.1)	142.7 (17.6)
Diastolic usual office BP (mmHg)[1]	80.4 (8.2)	74.9 (9.2)
Diabetes	35.1%	37.8 %
Hypertension	93.2 %	90.0 %
Myocardial infarction	5.4 %	13.3 %
Heart failure	4.1 %	5.6 %
TIA	8.1 %	6.7 %
CVA	8.1 %	11.1 %
PAD	6.7 %	14.4 %

Co-morbidity is based on ICPC coding in the problem list in the electronic patient record. eGFR =estimated Glomerular Filtration Rate. TIA=Transient Ischaemic Attack; CVA=cerebrovascular accident; PAD=peripheral artery disease. Values are given as mean and standard deviation or number (percentage).
[1] In one patient in the control group a usual blood pressure at baseline could not be found in the electronic patient file

Table 2 Outcome measures in the intervention and control group at t=1 year

Variable	Treatment goal	Control group	Intervention group	Difference for continuous variables (*odds ratio for discrete variables) between intervention and control group (95% Confidence Interval)	p=
N=		74	90		
Systolic study BP (mmHg)	<130 mmHg	142.9(16.8)	134.7(15.7)	-8.2 (-12.9 to -3.6)	<0.001
Systolic BP treatment goal reached (N,%)		*16(21.6)*	*40 (44.4)*	**2.9 (1.4 to 5.8)*	*0.003*
Δ systolic BP t=1 year minus t=0		*0.2 (95% CI -3.6 to 3.8)*	*-8.1(95% CI -11.3 to-4.8)*		
Diastolic study BP (mmHg)	<80 mmHg	80.9 (11.2)	73.8(9.6)	-4.7(-8.4 to -1.1)	0.01
Diastolic BP treatment goal reached (N,%)		*37 (50.0)*	*64 (71.1)*	**2.5 (1.3 to 4.7)*	*0.007*
Δ diastolic BP t=1 year minus t=0		*0.5 (95% CI -1.80 to 2.9) p=0.64*	*-1.1 (95% CI -3.2 to 1.0) p=0.30*		
Weight (kg)(SD)		80.8(15.0)	79.8(14.9)	-1.0 (-5.7 to 3.6)	0.72
Waist circumference (cm)	<80 female, <94 male	100.7(14.9)	101.2(12.9)	0.5 (-3.8 to 4.8)	0.23
Waist circumference, treatment goal reached(N,%)		*8(10.8)*	*5(5.6)*	**0.5(0.2 to 1.6)*	*0.22*
Creatinine (μmol/l)		114.2(24.6)	110.9(25.4)	-3.3 (-11.1 to 4.4)	0.64
e GFR MDRD (ml/min/1.73 m^2)		49.4(8.0)	48.6(8.7)	-0.7 (-3.3 to 1.9)	0.83
Fasting glucose (mmol/l)	<7	6.5(1.4)	6.4(1.4)	-0.1 (-0.6 to 0.3)	0.50

Table 2 Continued

Variable	Treatment goal	Control group	Intervention group	Difference for continuous variables (*odds ratio for discrete variables) between intervention and control group (95% Confidence Interval)	p=
N=		74	90		
Fasting glucose, treatment goal reached(N,%)		*58(78.4)*	*68(75.6)*	**0.9 (0.4 to 1.8)*	*0.67*
HbA1c (%)	<7	6.4(0.9)	6.4(0.8)	0.01 (-0.2 to 0.3)	0.88
HbA1c, treatment goal reached(N,%)		*63(85.1)*	*69(76.7)*	**0.6(0.3 to 1.3)*	*0.18*
Total cholesterol mmol/l		4.8(1.2)	4.6(1.1)	-0.2 (-0.5 to 0.2)	0.32
HDL cholesterol (mmol/l)		1.4(0.4)	1.4(0.4)	-0.04 (-0.2 to 0.1)	0.85
Total cholesterol/HDL		3.7(1.1)	3.6(1.2)	-0.04(-0.4 to 0.3)	0.55
LDLcholesterol (mmol/l)	< 2.5	2.6(1.1)	2.5(0.9)	-0.1 (-0.4 to 0.2)	0.57
LDLcholesterol, treatment goal reached(N, %)		*34(46.0)*	*47(52.2)*	**1.3 (0.7 to 2.4)*	*0.43*
Triglycerides (mmol/l)		1.8(0.8)	1.7(0.9)	-0.1 (-0.3 to 0.2)	0.32
Hemoglobine (mmol/l)	>6.8	8.9(0.8)	8.7(0.8)	-0.2 (-0.4 to 0.1)	0.36
Hemoglobine, treatment goal reached (N, %)		*74(100)*	*90(100)*	*n.a.*	*n.a.*
MCV (fl)		90.7(4.0)	91.7(4.0)[2]	0.9(-0.3 to 2.2)	0.06
serum albumin (g/L)	35-50	43.7(2.5)	43.3(2.3)	-0.5 (-1.2 to 0.3)	0.82
Serum albumin, treatment goal reached(N,%)		*73((98.7)*	*90(100)*	*n.a.*	*0.27*
Sodium (mmol/l)		140.8(2.7)	140.4(2.1)	-0.4 (-1.2 to 0.3)	0.42
Potassium (mmol/l)		4.38(0.42)	4.89(0.54)[1]	0.51 (0.36 to 0.66)	0.03
Calcium (mmol/l)	<2.54 l	2.32(0.12)	2.28(0.09)	-0.04 (-0.08 to -0.01)	0.05
Calcium, treatment goal reached (N, %)		*71(96.0)*	*90(100)*	*n.a.*	*0.05*
Phosphate (mmol/l)	<1.5 l	1.01(0.17)	1.04(0.14)	0.03 (-0.02 to 0.08)	0.66

Phosphate, treatment goal reached (N,%)		*74(100)*	*90(100)*	*n.a.*	-
PTH (pmol/l)	<7.7 ; if eGFR 15-30:<12	8.2(3.7)[2]	6.1(2.6)[3]	-2.1(-3.2 to -1.1)	0.02
PTH, treatment goal reached (N, %)		*43(59.73)*	*62(87.3)*	**3.2 (1.5 to 6.8)*	*0.002*
Urine albumin/creatinine (mg/mmol)	men<25 mg/mmol; women< 35 mg/mmol	6.8(33.4)[1]	3.9(6.6)[1]	-2.9(-10.8 to 5.0)	0.56
Urine albumin/creatinine, treatment goal reached (N, %)		*72(98.6)*	*82(97.6%)*	**0.6 (0.01 to 7.0)*	*0.68*
Body Mass Index (kg/m^2)	25	28.4(4.6)	28.9(4.7)	0.4 (-1.0 to 1.9)	0.68
Body Mass Index, treatment goal reached (N, %)		*13(17.6)*	*15(16.7)*	**0.9 (0.4 to 2.1)*	*0.88*
Smoking (number of patients smoking, (%)	Not smoking	10(13.5)	11(12.2)	n.a.	0.81
WONCA functional health status Overall health		3.0(0.8)[1]	3.0(0.8)[1]	-0.04 (-0.28 to 0.22)	0.42
Daily activities		1.7(1.0)[1]	2.1(1.2)[1]	0.34 (0.03 to 0.73)	0.27
Feelings		1.7(0.9)[2]	1.8(1.0)[1]	0.09 (0.98 to 0.16)	0.97
Physical fitness		3.1(0.8)	3.4(1.0)[1]	0.22 (-0.07 to 0.52)	0.15
Social activities		1.2(0.7)	1.6(1.0)[1]	0.33 (0.06 to 0.60)	0.12
Change in health		3.0(0.5)	2.8(0.6)[1]	-0.17 (-0.34 to -0.003)	0.06
Medication C09 agents acting on the RAAS system		47 (63.5)	73 (81.1)		0.01
Lipid modifying agents		38 (51.4)	66(73.3)		0.004
Vitamin D		1 (0.6)	14 (15.5)		0.002

BP=Blood Pressure in mmHg; missing values: [1]=1 missing value; [2]=2; [3]=3 etc;
RAAS=Renin-Angiotensin-Aldosteron-System; n.a.=not applicable
Values are given as mean and standard deviation (or standard deviation of difference) or number (percentage).

DISCUSSION

Summary

The shared care model for patients with CKD and diabetes or hypertension lead to a significant BP-lowering in the intervention group compared to the control group and a better achievement of BP-targets along with increased use of renin-angiotensin system inhibitors. The intervention also lead to lower PTH-levels along with an increased use of vitamin D and to an increased use of lipid lowering drugs. Although LDL-cholesterol decreased in the intervention group, LDL-levels at the end of the study did not differ between intervention and control group.

It is promising that BP-targets were better met in the shared care practices, because a lower BP is associated with better patient outcome.(6) Hypertension management is generally recognised as a primary care task, but BP-management in CKD-patients in primary care is not as effective as it is in nephrology.(26) Underlying factors are that the GP-confidence in treating CKD is lower than in treating diabetes and hypertension and that BP-targets in CKD are often regarded with scepticism.(27, 28) A discussion is ongoing on optimal BP-targets.(29) Systolic BP below 120mmHg is associated with stroke and diastolic BP below 60mmHg is associated with increased mortality in frail elderly.(30, 31) Nephrologists could be of help in the titration of antihypertensive agents.

Albuminuria did not change during our study. This was due to the fact that albuminuria treatment goals were already highly met at baseline. In a sub analysis we did not find albuminuria differences between diabetes and non-diabetes patients.

Strengths and limitations

A strength of the study is that it used a cluster randomised trial design. Usual care for diabetes and hypertension patients in the practices was already well organised, which makes the additive value of the shared care model robust. Baseline BP-values were at a relatively low level. In practices with less favourable baseline BP-levels, it may be possible to see even more improvement. We reduced potential bias in the usual care group by informing these patients, GPs and NPs at the end of the trial. The setting in research practices enabled retrospective collection of usual BP-measurements to serve as baseline measurements for the control group. A further strength is that, before entry, participants had two consecutive measurements of eGFR $<$ 60 ml/min/1.73 m^2 to confirm CKD-diagnosis.

Several limitations need to be mentioned. We followed a pragmatic recruitment procedure: when the maximum number of patients in one cluster was reached, we

stopped the inclusion in that practice. It may have caused a selection of relatively well-off patients who neatly obeyed to the control visits. On the other side, not all practices reached the required minimum of 20 patients. As a second limitation we should mention that we had to rely on usual BP-measurements to serve as baseline values. It is well known that usual BP-measurements lead to higher results than BP-measurements in a study-setting.(32) The fact that the usual BP-measurement in the control group did not differ from the study-BP at the end of the study reduces the concerns about comparability of usual and study BP-measurements in this trial. A third limitation is a potential selection bias because in the control group patients were asked informed consent one year after randomisation of their practice took place. However, they were identified at the beginning of the trial. A further point is about generalisability. One should realise that our population was mainly Caucasian, so our study results are not representative of a population with a greater proportion of non-Caucasian patients, who may have different BP outcomes. A final limitation is that cost-effectiveness was not evaluated in this trial and will require future study.

Comparison with existing literature

The effect of structured care by nurses was assessed in an observational study of Richards et al.(33) CKD-patients were enrolled in a disease management program. BP decreased with 9/5mmHg, but only in patients without diabetes or proteinuria. In secondary care, several studies have been performed on the role of nurses in the management of CKD-patients, with varying success. A study on elderly patients referred to a multidisciplinary care clinic with a nephrologist and a specialized nurse showed a 50% reduction of the risk for all cause mortality in an observational study.(34) In a comparison between additional intensive NP support and nephrologist care BP-decrease in the intervention group was 3/2mmHg more ($p<0.001$) than in the control group.(35) However, in a randomised trial where patients were randomly assigned to a nurse-coordinated team in secondary care or to usual care in general practice, no effect on cardiovascular risk factor control or on clinical end points was found.(36)

The opportunity to ask advice from a nephrologist has been studied in a shared care system in the United Kingdom.(17) Patients were treated in primary care sustained by continuous feedback by nephrologists on the laboratory and BP-results. BP decreased and prescribing of renin-angiotensin system inhibitors increased.

In summary, the existing literature endorses our findings that structuring care for CKD-patients is beneficial in reducing BP. However, study designs were mainly observational with consequentially low level of evidence. Cluster randomised trials like ours are scarce. We are awaiting the results of the QICKDstudy, a cluster

randomised trial to compare quality improvement interventions to lower systolic BP in CKD in primary care.(37) The results when published will provide interesting material to compare our data with.

Implications for research or practice

It is promising that an intervention of shared care showed BP-lowering during a one year intervention, even in practices that already had a well structured care for patients with diabetes or hypertension. Statements on more relevant endpoints like cardiovascular events and hospital admissions would need larger and longer cluster randomised trials. Future studies should provide information on cost-effectiveness. CKD has a high financial burden. As this model aims to provide optimal care at the cheapest level possible, it may prove to be cost-effective in lowering cardiovascular morbidity and mortality.

ETHICAL APPROVAL AND CONSENT

This study was performed according to the Code of Conduct for Health Research which has been approved by the Data Protection Authorities for conformity with the applicable Dutch privacy legislation and was in accordance with the Helsinki Declaration of 1975, as revised in 1983. Ethical approval was not required according to the accredited Medical Research Ethics Committee Arnhem/Nijmegen (ABR NL16590.091.07). Trial registration: Sharing study: SHARed care for patients In Nephrology And General practice; Netherlands Trial Registration TC 1140 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1140

Acknowledgements

Marjan Schoneveld and Wouter Koop of the laboratory of the Canisius Wilhelmina Hospital Nijmegen were very helpful in organising the laboratory tests.

We would like to thank the participating patients, the general practitioners and assistants of the NMP-practices. Furthermore we thank Lea Peters-van Gemert for the practical aspects of the trial and Reinier Akkermans for his statistical advice.

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Appendix 1 Overview of Blood pressure measurement results

	Baseline		T=1 year	
Parameter	Control	Intervention	Control	Intervention
N=	73	90	74	90
Systolic usual BP (mmHg)	142.5 (15.1)	142.7 (17.6)	n.a.	n.a.
Diastolic usual BP (mmHg)	80.4 (8.2)	74.9 (9.2)	n.a.	n.a.
Systolic study BP (mmHg)	n.a.	137.1 (16.5)	142.9 (16.8)	134.7 (15.7)
Diastolic study BP (mmHg)	n.a.	75.4 (10.7)	80.9 (11.2)	73.8 (9.6)

n.a.=not available; * missing values excluded

Appendix 2 Changes in outcome measures (other than BP) in intervention group between baseline and t=1 year. N=90

Variable	Baseline	t=1 year	Difference (95% confidence interval) between baseline and t=1 year	Significance
Weight (kg)	79.5(14.3)	79.8(14.9)	0.3 (-0.4 to 1.1))	0.34
waist circumference (cm)	101.3(12.7)	101.2(12.9)	-0.1 (-1.1 to 0.9))	0.79
Creatinine (μmol/l)	109.0(24.9)	110.9(25.4)	1.8 (-2.0 to 5.6)	0.34
e GFR MDRD (ml/min/1.73 m^2)	49.1(7.9)	48.6(8.7)	-0.5 (-1.9 to 0.9))	0.47
fasting glucose (mmol/l)	6.1(1.5)	6.4(1.4)	0.3 (0.07 to 0.53)	0.01
HbA1c (%)	6.3(0.7)	6.4(0.8)	0.07 (-0.01 to 0.14)	0.08
Total cholesterol (mmol/l)	4.9(1.1)	4.6(1.1)	-0.3 (-0.5 to -0.1)	<0.001
HDL cholesterol (mmol/l)	1.3(0.4)	1.4(0.4)	0.03 (-0.04 to 0.11))	0.40
Total cholesterol/HDL	4.0(1.2)	3.6(1.2)	-0.36 (-0.55 to -0.17)	<0.001
LDL_cholesterol (mmol/l)	2.9(1.0)	2.5(0.9)	-0.35 (-0.52 to -0.19)	<0.001
Triglycerides (mmol/l)	1.7(0.8)	1.7(0.9)	-0.01 (-0.16 to 0.14)	0.88
Hemoglobine (mmol/l)	8.8(1.0)	8.7(0.8)	-0.09 (-0.13 to 0.04))	0.17
MCV (fl)	91.8(3.7)[6]	91.7(4.0)[8]	-0.01 (-0.7 to 0.7))	0.97
Serum albumin (g/L)	43.3(2.3)[1]	43.3(2.3)	0.02 (-0.4 to 0.4)	0.91
Sodium (mmol/l)	140.1(2.2)	140.4(2.1)	0.33 (-0.12 to 0.79)	0.15
Potassium (mmol/l)	4.7(0.6)[2]	4.89(0.54)[2]	0.14 (0.02 to 0.26)	0.02
Calcium (mmol/l)	2.36(0.09)	2.28(0.09)	-0.08 (-0.10 to -0.06)	<0.001
Phosphate (mmol/l)	1.15(0.15)	1.04(0.14)	-0.10 (-0.14 to – 0.07)	<0.001
PTH (pmol/l)	6.2(3.5)[7]	6.1(2.6)[7]	-0.36 (-0.94 to 0.22)	0.22

Urine albumin/creatinine (mg/mmol)	3.0(5.7)[6]	3.9(6.6)[6]	0.78 (-0.20 to 1.76)	0.12
Body Mass Index (kg/m^2)	28.9(4.6)	28.9(4.7)	-0.04 (-0.30 to 0.21)	0.74
Smoking (number of patients smoking, %)	13(14.4)	11(12.2)		n.a.
WONCA functional health status: Overall health	2.9(0.9)[3]	3.0(0.8)[1]	0.10 (-0.10 to 0.31)	0.32
Daily activities	1.8(1.1)[4]	2.1(1.2)[1]	0.21 (-0.02 to 0.44)	0.07
Feelings	1.8(1.1)[3]	1.8(1.0)[1]	-0.01 (-0.24 to 0.21)	0.91
Physical fitness	3.5(0.9)[2]	3.4(1.0)[1]	-0.14 (-0.33 to 0.06)	0.17
Social activities	1.5(0.9)[2]	1.6(1.0)[1]	0.01 (-0.20 to 0.22)	0.91
Change in health	2.9(0.6)[2]	2.8(0.6)[1]	-0.08 (-0.25 to 0.09)	0.35
Agents acting on the RAAS system	66 (73.3%)	73 (81.1%)		0.02
Lipid modifying agents	53 (58.9%)	66(73.3%)		<0.001
Vitamin D	1(1.1%)	14 (15.5%)		<0.001

BP=Blood Pressure in mmHg; missing values: [1]=1 missing value; [2]=2; [3]=3 etc; RAAS=Renin-Angiotensin-Aldosteron-System
Values are given as mean and standard deviation or number (percentage).

4a

Population based screening for chronic kidney disease not cost effective; shared care in chronic kidney disease more attractive

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British Medical Journal, 16 December 2010

RAPID RESPONSE

Manns et al conclude that population based screening for chronic kidney disease (CKD) by eGFR measurement is not cost effective, unless used in patients with diabetes.[1] We can agree with their conclusion. Nevertheless, we would like to address a few of the assumptions made in this study, illustrated by initiatives in the management of chronic kidney disease in the Netherlands. By sharing treatment between primary and secondary care, costs could be less. By defining benefits a bit broader, the balance would be more positive than calculated.

First, chronic kidney disease is defined as a single health state by an eGFR below 60 ml/min/1.73 m^2. As prognosis is mainly affected in patients with eGFR below 45 ml/min/1.73 m^2, a worldwide discussion is ongoing concerning potential modification of the grading of chronic kidney disease. A subdivision of stage 3 CKD at 45 ml/min/1.73 m^2 has been proposed.2 Also age as a factor in the judgment of the grade of renal function is under discussion. The consequence of this growing insight is, that not all patients with an eGFR $<$ 60 ml/min/1.73m^2 require an expensive nephrologist visit. Daily practice is that general practitioners mainly refer patients with an eGFR $<$ 30 ml/min/1.73 m^2. [3,4] In the Netherlands, national guidelines have been developed to share the care for patients with CKD between primary and secondary care.[5] Screening is advised in high risk patients. Next the pragmatic advice is to refer patients with overt proteinuria or patients with eGFR $<$ 30 ml/min/1.73m^2 (age $>$ 65 years) or eGFR $<$45 ml/min/1.73 m^2 (age $<$ 65 yrs). Consultation of a nephrologist (without referral) is advised if eGFR is between 30 and 45 ml/min/1.73 m^2 in patients over 65 years or between 45 and 60 ml/min/1.73 m^2 in younger patients. In that way, the largest part of CKD stage 3 patients will be treated in primary care with support from a nephrologist. To facilitate this consultation, we developed Telenephrology, a webbased consultation aid. By Telenephrology, specialist's knowledge is transferred to primary care in a structured way. We studied 105 patients with diabetes and or hypertension in primary care with CKD stage 3 or worse. In this study, only two patients had to be referred from primary care to a nephrologist during one year. The others could be treated in general practice, with the aid of Telenephrology. This underlines the message of Gifford et al that screening will be less costly than suggested.[3]

A second aspect is the fact that the model only accounts for prevention of end stage renal disease and mortality. These outcomes are mainly associated with urinary protein loss. The benefits of reducing cardiovascular events in patients with reduced kidney function by treatment of hypertension[6] and lipid lowering are not included in the model of Manns. In the Sharp study (http://www.ctsu.ox.ac.uk/~sharp/slides.htm), lipid lowering in patients with reduced kidney function led to a reduction of 17%

in major atherosclerotic events. The reduction of cardiovascular morbidity might be more important than that of cardiovascular mortality. Data on multidisciplinary treatment of cardiovascular risk factors will be provided by the MASTERPLAN study that aims to reduce cardiovascular risk and to slow the decline of kidney function by a multifactorial approach in patients with moderate to severe CKD (stage 3 and 4) existing of a polydrug strategy and lifestyle treatment.[7]

Third, identifying decreased renal function could also lead to a better medication safety regime, provided that doctors and pharmacists take into account renal function in their drug prescribing. Impaired renal function appeared to be an important determinant in preventable medication -related hospital admissions.[8]

Our final remark is a small correction; Manns pointed that the Netherlands have an active population based screening program. This is not the case. This statement is probably based on a once only initiative of the Dutch Kidney Foundation in 2006 to provide people with urinary dipsticks for self-diagnosis of urinary protein loss.[9]

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5

Initial implementation of a web-based consultation process for patients with chronic kidney disease

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Annals of Family Medicine, vol 11, no 2, March/April 2013

ABSTRACT

Purpose A web-based consultation system (telenephrology) enables family physicians to consult a nephrologist on a patient with Chronic Kidney Disease: relevant data are exported from the electronic patient file to a protected digital environment from which advice can be formulated by the nephrologist. The primary purpose of this study was to assess the potential of telenephrology to reduce in-person referrals.

Methods In an observational, prospective study we analyzed telenephrology-consultations by 28 family practices and five nephrology departments in the Netherlands between May 2009 and August 2011. The primary outcome was the potential reduction in in-person referrals, measured as the difference between the number of intended referrals as stated by the family physician and the number of referrals requested by the nephrologist. Secondary outcome was the usability of the system, expressed as time invested, implementation in daily work hours and response time. Furthermore we evaluated the questions asked.

Results 122 new consultations were included. In the absence of telenephrology 43 patients (35.3%) would have been referred by their family physicians, whereas the nephrologist considered referral necessary in only 17 patients (13.9%) ($p<0.001$). The family physician would have treated 79 patients in primary care. In 10 of these patients the nephrologist deemed referral necessary. Time investment per consultation amounted to less than 10 minutes. Consultations were mainly performed during office hours. Response time was 1.6 days (95% CI: 1.2 – 1.9). Most questions concerned estimated glomerular filtration rate, proteinuria and blood pressure.

Conclusion A web-based consultation system might reduce the number of referrals and is usable. Telenephrology may contribute to an effective use of health facilities by allowing patients to be treated in primary care with remote support by a nephrologist.

INTRODUCTION

In 2002, the National Kidney Foundation released the 'Kidney Disease Outcome Quality Initiative' (K/DOQI) guideline for the evaluation and treatment of patients with chronic kidney disease (CKD) .[1] This guideline has been instrumental in improving the care of patients with CKD. According to the guideline definition the prevalence of CKD in the US has increased from 10% in 1994 to 13% in 2004.[2] In Western-Europe the prevalence of CKD is only slightly lower. [3,4] The widely implemented default laboratory reporting of estimated glomerular filtration rate (eGFR) has raised the awareness of CKD in primary and secondary healthcare, and, together with the increased prevalence, has increased the economic burden on the health care system. [5-7]

Cost-effective management of CKD patients requires that care should be given in a primary care setting where possible and in a secondary care setting where necessary. In the UK, the NICE guidelines on CKD provide family physicians (FPs) with tools to decide which healthcare setting, primary or secondary, is best suited for providing the patient's required care.[8] In the Netherlands, the interdisciplinary CKD-guideline for primary care and nephrology serves the same purpose.[9] To facilitate good care in a primary care setting, the advice of a nephrologist may be helpful and would limit referrals to only those that need an in-person referral.

Consultation between an FP and a nephrologist is traditionally performed by telephone or e-mail. The first may be inconvenient since a lot of detailed information has to be communicated, a report of the consultation is lacking and a timeslot that suits both doctors has to be found.[10,11] The latter is impractical because all relevant data must be transferred from the medical record to the e-mail message and most e-mail services are not sufficiently protected. Studies have reported electronic consulting where nephrologists had full access to the electronic health record of the patient.[12,13] This may raise privacy issues, as more information is available to the nephrologist than is necessary for the consultation.

To overcome these shortcomings, the Radboud University Nijmegen Medical Centre (RUNMC) Departments of Primary and Community Care and Nephrology have devised a web-based consultation system: telenephrology. FPs upload defined data that are relevant to CKD. These data are automatically extracted from the FP's electronic health record to a secured digital environment. FPs and nephrologists can use the system independently at a convenient time. The nephrologist gives treatment advice to the physician based on the patient's information, and by so doing, the need for referral may be reduced.

This observational study describes and analyzes the use of telenephrology by FPs and nephrologists. The primary objective was to assess the potential of telenephrology to affect referral rate. A secondary objective was to examine the usability of telenephrology by judging time investment, implementation in daily work and the nephrologist's response time. Finally, we explored the areas of patient care FPs were likely to consult about through telenephrology.

METHODS

The content of telenephrology was developed in the RUNMC by the Departments of Primary and Community Care and Nephrology. TeleMC, a company in telemedicine applications, was responsible for the technical development of the system. Telenephrology was introduced in 2009 in the RUNMC and five family practices. In 2011 it was expanded to a total of 28 family practices and five hospitals with nephrology care. This observational prospective study described and analyzed web-based consultations between May 2009 and August 2011 by 42 FPs and five nurse practitioners in 28 family practices and 14 nephrologists from five participating hospitals. Nurse practitioners worked on behalf of the FPs. We included all new consultations. In case the consultation resulted in recommendation for additional (diagnostic) testing, we also used the follow-up consultations to establish the outcome of the process. Data extraction was conducted by TeleMC for the variables shown in table 1. Data categorization was performed by VG and NS.

The usual referral process consisted of a face-to-face consultation between patient and nephrologist. The FP wrote a paper or electronic referral letter to inform the nephrologist and to request an appointment for the patient. Besides these regular referrals an FP could phone the nephrologist for advice. The FP's in our study had the choice to either refer the patient in the usual way or to consult a nephrologist by telenephrology and then, based on the advice given, decide how and where to manage the patient. The FP started the telenephrology-system directly from the patient file in the electronic health record. He logged on through a username and password. Essential patient data on medical history, medication, laboratory results and blood pressure, were automatically extracted from the patient's electronic health record and presented in an orderly manner. Where the FP judged part of the information presented not applicable, for example privacy-sensitive information, issues could be removed. Mandatory information that had to be filled out consisted of the actual question(s), whether or not the patient would have been referred if telenephrology were not available and time investment per consultation. The nephrologist was notified by e-mail or text message that a consultation had arrived,

logged onto the website, and advised based upon the information presented how to treat the patient in primary care, to refer, or to refer if additional diagnostic information met conditions specified by the nephrologist. The nephrologist could request additional information and defer management advice until this was available. Subsequently, the FP was informed in a similar manner when a reply had arrived. The reply was automatically noted in the electronic health record of the patient. The FP could then adjust patient care or refer the patient according to the nephrologist's advice. Requested additional information could be given in a follow-up consultation when new results had arrived. Moreover, the FP could ask for clarification or pose additional questions. A consultation about the same patient but addressing a new topic was considered a new consultation. An example of telenephrology-consultation can be viewed in web- appendix 1.

For the analysis, we were interested in the FP-decision to refer in relation to the telenephrology consultation. For this, we compared the referral decisions of the FP, had there not been the possibility of telenephrology, with the nephrologist's referral advice, which was considered as the gold standard. The nephrologist's advice to refer was collected from their entries in the web program. In case the nephrologist had requested additional information, the entry was taken from the follow-up consultation after receiving these data. We asked the FPs at every consultation whether the patient would have been referred to the nephrologist if telenephrology had not been available and, after the nephrologist-response, whether they would follow the referral advice given. We compared the referral rates with the recommendations as advocated by the Dutch interdisciplinary CKD-guideline for primary care and nephrology. To determine outcome significance between the FP intention to refer and the nephrologist's referral advice, McNemar's test was conducted for comparison of paired proportions using SPSS version 18.0 (IBM PASW statistics 18).

To assess usability we investigated time-investment, implementation in daily work-hours and response time. Time investment was reported by the professionals. Implementation in daily work-hours was defined by the timeslot in which the consultation took place: 06:00 – 08:00, 08:00 – 17:00, 17:00 – 19:00, or 19:00 – 06:00. This enabled evaluation of use during office hours, just before and after office hours, and at a later time during the day. The response time of the nephrologist was calculated in days.

For analysis of the questions asked, we firstly analyzed the individual questions with the intention to find categories and subcategories. Subsequently we allocated the questions to these (sub) categories. Each consultation could contain one or more questions.

To assess the satisfaction of the professionals with the system, we sent an online questionnaire in 2011 to the five practices that had used telenephrology during the pilot-phase in the previous year.

Ethics approval was not required according to the accredited Medical Research Ethics Committee Arnhem/Nijmegen (ABR NL16590.091.07).

RESULTS

Between May 2009 and August 2011, 125 new consultations were recorded, performed by 42 FPs and five nurse practitioners from 28 family practices. Three consultations were excluded because the FP used the system to get information on patients that had already been referred. The 122 included consultations concerned 116 patients. In 24 patients a total of 52 follow-up consultations were performed. Clinical characteristics of the patients are given in Table 1.

Referral

We compared the FP's intention to refer with the final referral advice of the nephrologist (table 2). The FPs intended to refer 43 patients. The nephrologists concluded that referral was not necessary and care could be delivered in primary care in 36 of these patients (84% reduction).

The opposite was seen in 10 patients, who according to the FP could be treated in primary care. The nephrologist advised referral for reasons of relatively young age (n=3), co-morbidity (n=1), proteinuria (n=2), rapid decline in renal function (n=2) and unspecified reason (n=2). The FPs agreed with all of the referral advice given, which meant a net referral reduction from 43 to 17(60.5%).

For comparison we also applied the recommendations given by the Dutch inter-disciplinary CKD-guideline for primary care and nephrology. Explanation of the guideline and comparison results are given in web-appendices 2 and 3.

Usability

Time investment per consultation amounted to 9 minutes for FPs and nephrologists. 73% of the FPs' use of telenephrology was between 08:00 – 17:00. 61% of the consultations were answered between 08:00 – 17:00.

The nephrologists' average response time was 1.6 days (95% CI: 1.2 – 1.9). 43% (n = 52) of all consultations were answered on the day of submission, 84% (n = 102) within 3 days. The full results are given in table 1.

Nine FPs answered the questionnaire. They all judged the amount and content of information that was sent by telenephrology appropriate. Ease of use was judged as

Table 1 Patient characteristics and time-investment in telenephrology consultations

New consultations (n = 122, unless specified otherwise)	**Distribution**
Age (years, range)	73.6 (34 – 96)
Gender Male/Female	40% (n = 49) / 60% (n = 73)
Estimated GFR (mL/min/1.73 m^2, range)	46 (22 – 128)
Albuminuria	Normoalbuminuria 49% (n = 48) Microalbuminuria 38% (n = 38) Macroalbuminuria 13% (n = 13)
Date of consultation	01/05/2009 – 09/08/2011
Time of consultation FP	06:00 – 08:00 1% (n = 1) 08:00 – 17:00 73% (n = 89) 17:00 – 19:00 17% (n = 21) 19:00 – 06:00 9% (n = 11)
Time of consultation nephrologist	06:00 – 08:00 1% (n = 1) 08:00 – 17:00 61% (n = 74) 17:00 – 19:00 25% (n = 31) 19:00 – 06:00 13% (n = 16)
Time investment FP, minutes	9:27 (95% CI, 8:29 to 10:25)
Time investment nephrologist, minutes	8:45 (95% CI, 8:04 to 9:27)
Days until response	1.6 (95% CI, 1.2 to 1.9)
Follow-up consultations (n=52)	
Time investment FP (minutes)	6:43 (95% CI 5:48 to 7:38)
Time investment nephrologist (minutes)	6:47 (95% CI 5:55 to 7:40)

Consultations performed by 42 family physicians and 5 nurse practitioners in 28 family practices.

reasonable (2/9) to good (7/9). They found it reasonably easy (4/9) to easy (5/9) to fit the use of telenephrology within daily practice work. Eight out of nine users said that their knowledge of nephrology had increased by the use of telenephrology. The two nephrologists found the data supplied sufficient to get a good view on the patient's case. In the future they would like the data to be graphically presented. The nephrologists could see a learning curve in the way FPs asked questions.

Table 2 Intended referral by family physicians and referral advice from nephrologist

	Nephrologist advises referral		Nephrologist advises primary care			
FP has intention to refer	7	(5.7%)	36	(29.5%)	**43**	**(35.3%)**
FP wants to treat in primary care	10	(8.2%)	69	(56.6 %)	**79**	**(64.8%)**
	17	**(13.9%)**	**105**	**(86.1%)**	**122**	

McNemar's test comparing FP intention to refer and the nephrologist's referral advice: $p<0.001$.

Table 3 Categorization and distribution of the questions of the family physician

Main group	Subject	N
Intrinsic kidney disease 60% (n = 124)	Decreased estimated GFR	19
	Decreasing estimated GFR	30
	Micro albuminuria	14
	Macro albuminuria	6
	Blood pressure in relation to CKD	23
	Unspecified	32
Metabolic complications 27% (n = 55)	Bone and mineral metabolism	42
	Hemoglobin	12
	Acid-base homeostasis	1
Cardiovascular Risk Management 4% (n = 9)	Diabetes	5
	Cholesterol	4
Comorbidity in relation to CKD 8% (n = 16)	Gout	1
	Urinary tract infection	1
	Patients condition	3
	Drugs that interact with impaired kidney function	11
Other 1% (n = 3)	Cardiomyopathy	2
	Urinary tract infection	1

Consultation content

The result of the categorization of question topics is displayed in table 3. The nephrologist addressed the question in a broader context and provided advice not specifically asked for in 35% (n = 43) of the answers. This advice mainly considered medication safety in relation to renal function and advice to check the patient for mineral and bone disorder (secondary hyperparathyroidism, Calcium, Phosphorus, vitamin D) or for anaemia.

DISCUSSION

Our data provide support for the introduction of telenephrology in primary care. The intended referral rate by the FP was far higher than that advised by the nephrologist. This could result in a more convenient care at lower health care costs.

Telenephrology and other electronic consultation systems

Several other studies have described the use of electronic consultation technology in the management of patients with CKD. In Hawaii, nephrologists proactively intervened in primary care by using data from Kaiser Permanente's electronic medical system and by providing unsolicited advice to FPs.[12] Their intervention lead to an increase in timely referrals and a reduction in low risk referrals. This initiative was nephrologist driven, and was possible only because nephrologists had entry to all electronic health records. This meant that they had access to irrelevant data, which is not desirable both from an efficiency and a privacy point of view. In the United Kingdom, Stoves et al. set up an e-mail referral system for patients with chronic kidney disease: if the GP referred the patient by e-mail, the patient was asked to provide consent for the nephrologist to look in the electronic health record.[13] Based on the information read, the nephrologist advised referral or gave management advice to be carried out in the primary care setting. This lead to a reduction in referrals from 30 to eight patients (73% reduction), similar to our primary outcome. The mean response time was 7 days and mean time needed for the consultation was 15.5 minutes. The time required in our study was less, which is probably because only relevant pre-formatted information was presented.

Patient benefits

Depending on the extent to which FPs pose questions by telenephrology, patients might receive more adequate care in relation to blood pressure, hyperparathyroidism, anaemia and medication safety. This will most probably affect patient survival and morbidity.[14-16] Furthermore, patients can be referred for predialysis care more timely if FPs and nephrologists monitor CKD progress team wise.[17] The convenience for

patients lays in quicker specialist responses than with a usual referral, prevention of time-consuming hospital visits and the fact that they do not need to see another doctor. Although we did not study this, we expect a higher patient satisfaction if treatment can be given in a patients' own environment. This was demonstrated in a study on joint teleconference consultations.[18]

Economic benefits

Telenephrology has the potential to reduce referrals and so could contribute to a cost reduction. A usual referral cost €600,-. A telenephrology consultation cost €107, including a nephrology tariff and the online facilities. Each prevented referral meant a saving of €493. Additional costs in primary care should be evaluated. Pan et al examined telehealth models in a simulation study and found that physician-to-physician consultation systems can contribute to a substantial cost reduction. [19]

As indicated by our data, the introduction of telenephrology may also lead to referrals that were not primarily intended by the FP, but where the nephrologist deemed a referral necessary. In these cases, the higher costs of referrals are likely to be balanced by lower costs related to earlier detection and treatment of kidney disease.

Broadening the concept

We think that e-consultation offers the ability to break down walls between primary and specialist care. It facilitates shared care in patients with chronic disease conditions and it might enable effective use of expensive secondary care facilities. Joint teleconference medical consultation is a promising development as well, but has the disadvantage that both FP and specialist must be available at the same time-slot. Furthermore, it does not provide documentation in the electronic health record. Where interprofessional consultation relies mainly on measurable and preformulated data, web-based consultation seems more practical and effective than a referral or teleconferencing.

Limitations

We must consider some limitations of this study. The web-based consultation aimed to lead to more appropriate referrals to the nephrologist and the primary outcome measure was whether intended referral rate decreased. It will be important to assess how robust this is, or whether at a later date patients are referred despite the consultation. On the subject of referrals we merely analyzed the intention to refer. There were no data available on the actual number of referrals following this advice. These data will be generated in a cluster randomized controlled trial on the influence of telenephrology on the actual rate of referrals: the CONTACT study (Consultation Of Nephrology by Telenephrology Allows optimal Chronic kidney disease Treatment

in primary care, Netherlands Trial Registration code 2368). In this trial the effect of telenephrology on the actual referral rate and the quality of care will be evaluated. This study will enable a direct comparison between referrals in practices using telenephrology and those not, providing better evidence than the current study which used an internal gold standard.

Data on professional behavior (for example referral) are subject to clustering within professionals, for which we did not correct in this usability study.

The generalizability of the telenephrology technique depends on local settings. At the very least the primary care physician must use an electronic health record which allows automatic data extraction. Although it might be possible to create a similar system that allows direct data entry by the FPs, this is prone to errors and certainly not time efficient.

We did not evaluate patient satisfaction, which is a limitation. The satisfaction of the professionals was measured in an early stage of the study, so only included five practices. The data are too small to interpret, but the opinion tends to be positive. In the implementation of tele-health, the applicability in daily work proved to be very important.[20,21] With that in mind, it is favorable that the telenephrology system fitted in the daily work routine: most doctors used the system during office hours, spending less than 10 minutes on a consultation and nephrologists responded quickly.

In conclusion, a web-based consultation system might reduce the number of referrals by enabling FPs to receive suitable advice from nephrologists. The system is usable for both nephrologist and FP and allows efficient care of patients with CKD in primary care.

Acknowledgements
We thank the participating family practices and nephrologists in the Canisius Wilhelmina Hospital Nijmegen, Gelderse Vallei Hospital Ede, Rijnstate Hospital Arnhem, Bernhoven Hospital Oss/Veghel and Radboud University Nijmegen Medical Centre.
TeleMC technically developed the telenephrology system and extracted the data.
Lea Peters, research assistant, supplied the family practices if necessary with technical support.
We thank Helen Atherton, researcher at the National School of Primary Care Research Oxford, for critically reading the manuscript.

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WEB APPENDIX 1

Example of a telenephrology consultation

Name patient :	XXX
Date of birth :	X-X-1934
	Male

CONSULTATION

Name Family Physician XXXXXX, date of consultation, X-X-2011, 13.20

Medical history :	14042011 Chronic Kidney Disease 27032009 Smoking stopped in 1962 27102001 Hypertension 19051995 Choreoideamelanoma OD 23111998 Diabetes mellitus type 2,
Actual medication:	31032011 METFORMINE 500MG TABLET 2D2T 31032011 SOTALOL HCL ACTAV 80MG TABL 1D1T 31032011 SIMVASTATINE 40MG TABLET FO 1D1T 31032011 GLIMEPIRIDE RP 3MG TABLET 1D1T 31032011 LISINO/HYDTHIA SD 20/12,5 T 1D1T 31032011 ACETYLSAL CARD CF 80MG DISP 1D1T 14042011 AMLODIPINE RP TABLET 5MG 14.0 1D1T
Medication changes in last 4 months?	No
Auto-medication (NSAIDS) :	No
Referral	unknown

physical examination	31-03-2011	01-02-2011	30-12-2010	04-10-2010	01-07-2010	01-04-2010	29-12-2009	30-09-2009
Weight	77 kg	77.6 kg	77 kg	75.8 kg	75.8 kg	75.5 kg	77.6 kg	76.4 kg
BMI			25					
Length			176					
Smoking						before		

RR	31-03-2011	22-03-2011	01-02-2011	30-12-2010	04-10-2010	01-07-2010	01-04-2010
RR syst	164 mmHg	138 mmHg	149 mmHg	161 mmHg	140 mmHg	142 mmHg	146 mmHg
RR diast	88 mmHg	87 mmHg	85 mmHg	87 mmHg	81 mmHg	75 mmHg	68 mmHg

	17-06-2009	27-03-2009	30-12-2008	30-09-2008	03-06-2008	03-04-2008	03-01-2008	05-10-2007	17-08-2007	06-07-2007
	76,0 kg	78,1 kg	77,6 kg	77,3 kg	77,0 kg	78,0 kg	77,9 kg	76,8 kg	77,0 kg	78,3 kg

	29-12-2009	30-09-2009	17-06-2009	30-12-2008	08-12-2008	30-09-2008	03-06-2008	03-04-2008	06-07-2007
	149 mmHg	140 mmHg	144,0 mmHg	151,0 mmHg	172,0 mmHg	135,0 mmHg	143,0 mmHg	152,0 mmHg	137,0 mmHg
	78 mmHg	76 mmHg	70,0 mmHg	89,0 mmHg	84,0 mmHg	81,0 mmHg	76,0 mmHg	74,0 mmHg	82,0 mmHg

Laboratory results	08-04-2011	25-03-2011	22-03-2011	01-02-2011	30-12-2010	26-03-2010
Creatinine	151 micromol/l	141 micromol/l				101 micromol/l
eGFR MDRD	42 ml/ min/1,73m2	45 ml/ min/1,73m2				>60 ml/ min/1,73m2
Fasting glucose		8,0 mmol/l	10.4 mmol/l	10.4 mmol/l	13.8 mmol/l	8,6 mmol/l
HbA1c		60 mmol/l				64 mmol/l
Tot chol		2,8 mmol/l				2,5 mmol/l
HDL		0,7 mmol/l				0,8 mmol/l
LDL		1,5 mmol/l				1,2 mmol/l
Chol/HDL		3,9				3,2
TG		1,44 mmol/l				1,13 mmol/l
Hb	7,8 mmol/l					
MCV						
Albumin						
Sodium		138				139
Potassium		3,6 mmol/l				3,7 mmol/l
Calcium	1,2 mmol/l					
Phosphate	1,4 mmol/l					
PTH	6,2 mmol/l					
Vitamin B12						
Folic acid						
Ferritin						
Serum-iron						
Iron binding capacity						
Transferrin						
Vitamin D						
Urea						
Bicarbonate						

07-04-2009	27-03-2009	02-07-2008	03-06-2008	28-03-2008	29-08-2007	20-08-2007
103,0 micromol/l				95,0 micromol/l		94,0 micromol/l
60,0 ml/ min/1,73m2				60,0 ml/ min/1,73m2		60,0 ml/ min/1,73m2
10,1 mmol/l	11,8 mmol/l	8,4 mmol/l	8,8 mmol/l	9,0 mmol/l		6,3 mmol/l
2,7 mmol/l				2,4 mmol/l		
1,1 mmol/l				1,1 mmol/l		
1,2 mmol/l				0,9 mmol/l		
2,6				2,2		
0,96 mmol/l				0,96 mmol/l		
					8,0	7,8
					93,0	92,0
138,0				140,0		138,0
3,8 mmol/l				3,8 mmol/l		3,4 mmol/l
					70,0	

Urine	25-03-2011	26-03-2010	07-04-2009	28-03-2008
Tot protein urine				
Alb/creat ratio	2,1 mg/mmol	1,0 mg/mmol	0,2 mg/mmol	0,6 mg/mmol
creatinine urine	8,4	8,1	3,8	8,8
Albumine urine				
Sediment	normal			

Question :	Dear colleague, I saw this patient for his annual diabetes control. MDRD appeared to be decreased from > 60 to 45 ml/min/1.73 m^2. Two weeks later the MDRD was 42 ml/min/1.73 m^2. In the anamnesis I did not find a reason: no NSAID use, no recent medication change. The alb/creat ratio increased, but is still normal. Blood pressure is higher than before; I added amlodipine 5 mgr. I plan to refer this patient. What should I do meanwhile?
If telenephrology were not available, would you refer the patient?	● Yes ○ No
Answer	

XXXXX, nephrologist, XXXXXXXX hospital

Date X-X-2011, 15.30	Dear colleague, The fact that this patient does not have proteinuria, makes it plausible that the decrease in renal function has a prerenal cause, a tubulointerstitial nefritis (TIN), or a post-renal cause (prostate hypertrophy/retention?). Do you have an ultra sound of kidneys and bladder? A TIN could be caused by hydrochlorthiazide. The combination enalapril/HCT increases the risk of acute kidney injury in case of dehydration or fever. I suggest that you stop lisinopril/HCT for 2 weeks and increase the dose of the Ca-antagonist, if the blood pressure rises. Please get in touch by Telenephrology after 2 to 3 weeks to report eGFR. Take care: metformin 2x1000mg is too high for this renal function; 2x 500mg is the limit. Glimepiride can be increased to 6 mg. The sotalol dose is rather high.
Patient should be referred to a nephrologist:	○ Yes ○ No ● No, unless:
	Renal function is not ameliorating after medication change
How much time did you need to fill in the form?:	10 minutes

ADDITONAL MESSAGES

Message from *family physician*	● I will follow your advice ○ I will not follow your advice, because…….
XXX *dd X -X-2011 17:32*	Dear colleague, I will order an ultrasound of kidneys and bladder. I will change the medication conform your advice and I will report in a follow-up consultation

WEB APPENDIX 2

Dutch interdisciplinary CKD-guideline for primary care and nephrology: recommendations for the care of patients with CKD

	normo / microalbuminuria	macroalbuminuria
Patients > 65 years of age		
eGFR > 60 ml/min/1.73m2		
eGFR 45 – 60 ml/min/1.73m2		
eGFR 30 – 44 ml/min/1.73m2		
eGFR < 30 ml/min/1.73m2		
Patients < 65 years of age		
eGFR > 60 ml/min/1.73m2		
eGFR 45 – 60 ml/min/1.73m2		
eGFR 30 – 44 ml/min/1.73m2		
eGFR < 30 ml/min/1.73m2		

Gray: evaluation and treatment in primary care.
Light Gray: consultation of a nephrologist (without referral).
Dark Gray: referral to secondary care.

Adapted from Grauw de W, Kaasjager HAH, Bilo HJG, Faber EF, Flikweert S, Gaillard C, et al. Landelijke Transmurale Afspraak Chronische nierschade, http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_samenwerking/k_ltas.htm (*with permission of the Dutch College of General Practitioners).*

WEB APPENDIX 3

The FP's intention to refer compared to the nephrologist's referral advice plotted against the Dutch interdisciplinary CKD-guideline for primary care and nephrology.

Dutch CKD-guideline (could only be applied to patients with urine assessment)	Family physician	Nephrologist
referral to secondary care n = 23	Refer n=12	Refer n = 6
Consultation of a nephrologist n = 43	Refer n = 15	Refer n =7
treatment in primary care n = 33	Refer n = 10	Refer n =0

6

A pharmacy medication alert system based on renal function in older patients

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Br J Gen Pract. 2012;e525-e529

ABSTRACT

Background Patients with diabetes or cardiovascular disease are at risk for reduced renal function and frequently use drugs that interact with renal function. General Practitioners (GPs) monitor renal function in these patients. Computerised prescription systems produce alerts in patients labelled as having chronic kidney disease, but alerts are often ignored. If pharmacists use a pharmacy medication alert system (PMAS) based on renal function, they can provide the GP with therapeutic advice to optimise the medication. The extent of this advice and the feasibility in the clinical context are unknown.

Aim To assess the therapeutic advice formulated by pharmacists with help of a PMAS based on the renal function of patients aged ≥70 years with diabetes or cardiovascular disease.

Design and setting Observational study in primary health care in the Netherlands.

Method GPs provided pharmacists with the renal function of older patients with diabetes or cardiovascular disease who were using target drugs, that is, drugs requiring therapeutic advice in patients with reduced renal function. With the help of a PMAS, pharmacists assessed the actual medication. The GP weighed the advice in relation to the clinical context of the individual patient.

Results Six hundred and fifty patients were prescribed 1333 target drugs. Pharmacists formulated 143 therapeutic recommendations (11% of target drugs) concerning 89 patients (13.7% of study population). In 71 recommendations in 52 patients (8.0% of study population), the GP agreed immediately.

Conclusion The use of a PMAS resulted in therapeutic advice in 11% of the target drugs. After weighing the clinical context, the GP agreed with half of the advice.

INTRODUCTION

Chronic kidney disease (CKD) is a growing health problem, with a prevalence from 4.9% in general practice in the UK to up to 13% in the US population.[1-3] The medical consequences of CKD are not only the risk of end-stage renal disease and cardiovascular morbidity, but also an increased risk of adverse drug events and medication-related hospital admissions.[4,5]

When renal function is reduced, the dosage of drugs that depend on renal excretion should be adjusted and nephrotoxic drugs should be avoided.[6-8] Patients with diabetes and cardiovascular disease have an augmented risk of CKD and frequently use renally cleared drugs.[1,9] Medication alerts systems warn prescribers of medication that can interact with impaired renal function, but these alerts are often ignored.[10-13] A medication alert system that weighs the actual renal function of the patient could help to reduce medication errors.[14-16]

This observational study assessed the therapeutic advice formulated by the pharmacist with help of a medication alert system based on the renal function of patients aged ≥70 years with diabetes or cardiovascular disease.

METHOD

Setting and study population

The study was conducted in Arnhem, a city in the East of the Netherlands with nearly 148 000 inhabitants. Seven GPs, belonging to the same pharmacotherapy audit meeting group, participated in the study. Five pharmacists who worked in close collaboration with this group selected the patients in their pharmacy computer system. Patients aged ≥ 70 years in the care of the participating GPs were eligible if they were on GP-prescribed maintenance therapy of blood-glucose-lowering or cardiovascular drugs (for example, digoxin, diuretics, or inhibitors of the renin-angiotensin system (RAS), including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)). Patients also used at least one 'target drug' on the inclusion date of 4 January 2010. 'Target drugs' were defined as drugs requiring therapeutic advice in patients with decreased renal function considering the Dutch dosing guideline for impaired renal function.[17] Patients with an estimated glomerular filtration rate (eGFR) < 10 ml/min/1.73m^2 were excluded (Figure 1).

The GPs already used a computerised medication monitoring system. This system generated an alert when the GP prescribed a target drug in patients labelled as having CKD, but it could not consider the eGFR level.

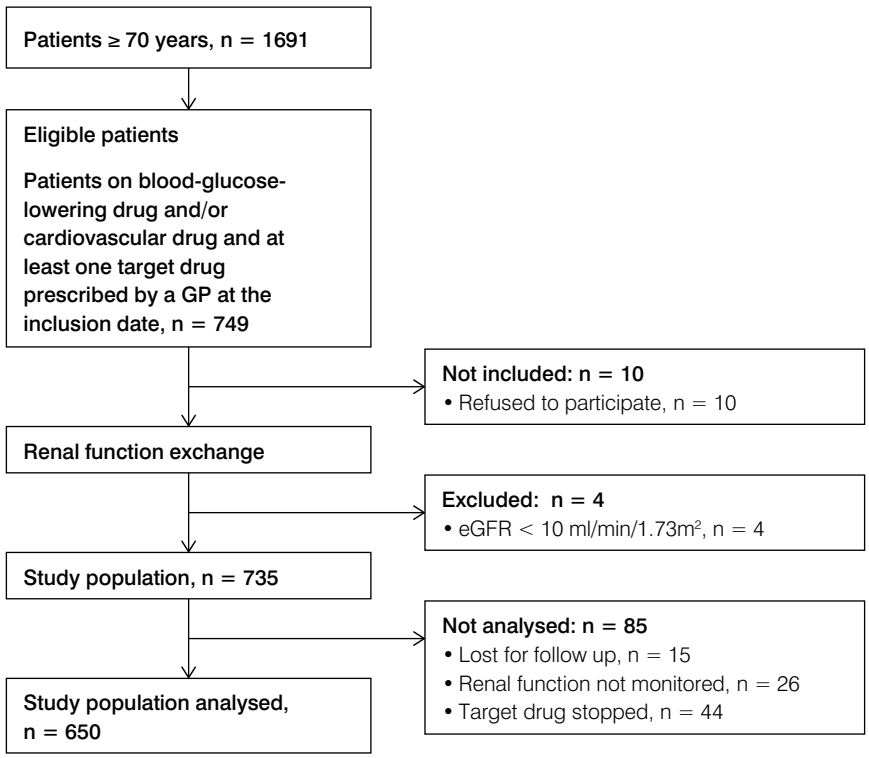

Figure 1 Selection of the study population

The use of drug dispensing data and laboratory test results in this study complied with Dutch privacy regulations.

Renal function monitoring

Actual eGFR was defined as an eGFR value measured within the last 12 months. If an actual eGFR was unknown, the GP requested the patient to undergo a blood test for renal function. The laboratory provided serum creatinine and an eGFR (ml/min/1.73m^2) calculated by the normalised four-variable Modification of Diet in Renal Disease (MDRD).[18] Serum creatinine was measured enzymatically (Modular, Roche diagnostics) and was IDMS (isotope dilution mass spectrometry) calibrated. The actual values of eGFR data were provided to determine drug-specific risk.

Assessment of renal function alerts

In this study, the pharmacists used a pharmacy medication alert system (PMAS) built by one of the authors (AG) in a Microsoft® Access database. The system, which was an addition to the current pharmacy computer system, assessed the medication in relation to the reported eGFR and provided an alert for target drugs according to the Dutch guidelines for drug administration in reduced renal function.[17] These guidelines include drug-specific cut-off values for eGFR, accompanied by a therapy- adjustment advice.

After receiving a data file from the GP with the eGFR of the included patients, the pharmacists linked the eGFR in the PMAS. Simultaneously, the patient's actual medication was electronically imported from the usual pharmacy computer system into the PMAS. An alert was generated to stipulate action if the eGFR was lower than the cut-off value of the target drug (Table 1). The software could not correct for invalid dose or dose interval, so the pharmacist assessed the alerts for these aspects based on the guideline recommendations presented in a text box. The pharmacist formulated therapeutic advice for either dosage adjustment, to stop the drug, or to substitute it by a non-contraindicated drug. Once a week, the pharmacist communicated the therapeutic advice to the GP by a list. The GP evaluated the therapeutic advice in relation to the clinical context of each individual patient, and responded with agreement or disagreement. Predefined reasons for disagreement could be checked on the list and the GP was asked to give supplementary comments in a free-text box. The list was returned to the pharmacist.

Outcome

The outcome of the study was the frequency of therapeutic advice formulated by the pharmacist (expressed as a proportion of the total number of target drugs). The management of the therapeutic advice by the GP was also studied.

Statistical analysis

All relevant patient data were entered into a Microsoft Access 2003 database and further analysed with SPSS Statistics (version 17.0) for descriptive statistics (mean, frequency, range).

RESULTS

On the inclusion date 650 patients were included and analysed (Figure 1). These patients were prescribed 1333 target drugs (Table 2). An actual eGFR had been determined in 78.5% (n = 510) of the patients (range per GP 66-89%). In the remaining patients, eGFR was determined after the inclusion date.

Table 1 Predefined cut-off values top 10 target drugs with truncated guideline advice

Therapeutic group	Drug name	Cut-off values ml/min	Guideline advice
Blood-glucose-lowering drugs	Metformin	30-50	Initial dose 2x 500 mg
		<30	Contraindicated
	Glimepiride	10-50	Initial dose 50%
Cardiac glycosides, digoxin	Digoxin	10-50	Intial dose 50%
Low-ceiling diuretics, thiazides	Hydrochlorothiazide	30-50	Initial dose 12.5 mg
		<30	Contraindicated
High-ceiling diuretics	Furosemide	10-30	Dose higher
Potassium-sparing diuretics	Spironolactone	10-50	Monitor potassium
	Amiloride	30-50	Monitor potassium
		<30	Contraindicated
Diuretics combinations	Triamterene	30-50	Dose 50%, monitor potassium
		<30	Contraindicated
	Epitizide	<30	Contraindicated
Beta-blockers	Sotalol	30-50	Max dose 160 mg/day
		10-30	Max dose 80 mg/day
Angiotensin-converting enzyme inhibitors	Enalapril	30-50	Intial dose 5 mg
		10-30	Intial dose 2.5 mg

Table 2 Characteristics of the analysed study population

Characteristics	n	%
Patients	650	100.0
Female	433	66.6
Target drugs	1333	
	Mean	**SD [range]**
Age, years	81	6.7 [70-101]
eGFR, ml/min/1.73m^2	63,3	17.0 [13- >95]
Number of drugs	5,8	2.8 [1-17]
Number of target drugs	*2*	1.1 [1-7]
Patients prescribed target drugs by therapeutic group	**n**	**%**
Blood-glucose-lowering drugs	156	24.0
Cardiac glycosides digoxin	73	11.2
Low-ceiling diuretics thiazides	259	39.8
High-ceiling diuretics	164	25.2
Potassium sparing diuretics	49	7.5
Diuretics combinations	46	7.1
Beta-blocker sotalol	33	5.1
Beta-blockers atenolol/bisoprolol	31	4.8
RAS-inhibitors	224	5.1

eGFR = estimated glomerular filtration rate. RAS = renin-angiotensin system.
SD = standard deviation

Assessment of renal function alerts

The computer software generated 212 alerts (15.9%) in a total of 1333 target drugs, because the eGFR was lower than the predefined cut-off value of the target drug. After the pharmacist assessed the actual medication for correct dose and dose interval, 93 alerts (7.0%) appeared to be correct and seven alerts (0.5%) were missing. Therefore, action to adjust therapy was considered necessary in 112 prescriptions in 74 patients (8.4% of the target drugs, 11.4 % of the patients). Additionally, pharmacists gave advice in 31 prescriptions of target drugs, even though the eGFR was just above the cut-off value. Eventually, 143 therapeutic recommendations (10.7% of the target drugs) concerning 89 patients (13.7% of analysed study population) were included for analysis of the GP responses. The drugs most frequently involved were diuretics

(41.3% of therapeutic advice), blood- glucose-lowering drugs (14.0%), digoxin (11.2%), and RAS inhibitors (10.5%). Almost all prescriptions that received an alert were chronic prescriptions taken by the patient for a longer period of time.

GP response to pharmacist advice

The GP immediately agreed with 71 recommendations (49.7% of the therapeutic advice) concerning 52 patients (8.0% of the study population).The GP most frequently disagreed with the advice on diuretics, blood-glucose-lowering drugs, digoxin, and RAS inhibitors. Within each of these therapeutics groups, the GP immediately disagreed in one-third of the advice. The responses of the GPs are shown in Table 3.

Table 3 GP response

Response	n (total N=143)	%	Comments
Immediate agreement	71	49.7	52 patients, 8% of study population
Postponed reaction	20	14.0	-
• GP first wants to consult specialist	12	8.4	-
• GP first wants to speak to patient	6	4.2	-
• Further monitoring biomarker(s)	2	1.4	Potassium, creatinine
Disagreement	38	26.6	-
• No standard reason indicated	17	11.9	No adverse reactions (n=1), already low dose (n=2)
• Potassium normal	5	3.5	
• Disease is stable	16	11.2	Diabetes (n=5), heart failure (n=7), hypertension (n=3), renal function (n=1)
Specialist is treating patient	14	9.8	Specialist was responsible for the drug therapy (GP only prescribed the refill prescriptions)

DISCUSSION

Summary

The use of a PMAS based on renal function resulted in therapeutic advice for a substantial number of drugs in older patients with diabetes or cardiovascular disease. The GP immediately agreed with half of the advice. Overall, in 5% of the prescriptions, the GP agreed to rectify the prescription.

The GPs used a medication monitoring system based on the Dutch G-standard,[17] the national drug database, which is used by all professional parties in Dutch health care. Despite this monitoring system, pharmacists still formulated additive therapeutic advice in 11% of the target drugs. What could be the reasons for this? First, it is known that a high number of medication alerts may cause 'alert fatigue' in the prescriber.[10] In the case of repeat prescriptions in particular, alerts were ignored. The extra effort to seek a renal function and to weigh the choice and dosage of the drug may cost too much time. Second, this observation could be explained because at the time of prescription, an actual eGFR was not available in more than 20% of the patients. Finally, it is important to consider the prescribing context. The alerts concerned chronic medication that the patient may have been using for a longer period of time, with an established clinical effect and with the patient accustomed to take them. Change of drug choice under these circumstances may disrupt the flow of treatment. The use of PMAS reduced the number of alerts compared to the current pharmacy computer system. A more sophisticated clinical decision support system could further reduce the number of irrelevant alerts by incorporating invalid dose or dose-interval algorithms that can weigh comorbidity and other patient-related risk factors that may affect the reliability of the eGFR,[19] and by linking laboratory to pharmacy data. Currently, some of these principles are already incorporated in new versions of medication monitoring systems.

Strengths and limitations

This study revealed the benefit of therapeutic advice automatically generated by a PMAS based on renal function. The clinical relevance is substantial: prescribing of target drugs to older patients with diabetes of cardiovascular disease is a daily activity in primary care, and the risk of complications related to renal function is high.[4] Primary care studies on compliance to dosing guidelines in patients with CKD are rare.[6] Recently, Bhardwaja et al demonstrated in a large US study of 32 917 patients with an eGFR below 50 ml/min/1.73m^2, that an alert system in the pharmacy can result in a reduction of medication errors from 49% to 33%.[14]

The data may not be generalisable to other settings because of the small number of participating practices, but the underlying problem of medication safety in relation to renal function and the intervention of a PMAS is of general interest.

The advice given was based on a single eGFR value obtained not more 1 year previously. This was for pragmatic reasons: renal function of patients who are in a diabetes or hypertension control system should be monitored yearly. However, variability in serum creatinine measurements necessitates at least two creatinine measurements,[20,21] and even more frequent monitoring of renal function is needed in patients who are not stable.[22]

Comparison with existing literature

GPs immediately agreed with half of the therapeutic advice. This is in accordance with the acceptance rate in a study in which clinical pharmacists gave therapeutic recommendations to GPs based on the medical records of 200 patients with diabetes or hypertension.[23] In a hospital setting, the acceptance rate was the same: 55% of the pharmacist advice was accepted by the clinician.[15]

Besides the predefined reasons for disagreement, the GPs were not very explicit with their comments in the free-text box. Disagreement could be explained by a difference between the dosage guidelines and clinical practice. An example is the advice to start with low doses of RAS inhibitors to prevent adverse drug reactions, whereas current clinical practice guidelines do advise to prescribe RAS inhibitors in high doses in order to protect kidney function (with monitoring of renal function and serum potassium).[24-26] Meanwhile, the advice in the Dutch dosage guidelines has been adjusted to clinical practice.

Implications for research and practice

To optimise drug prescribing in patients with decreased renal function, many steps need to be taken: systematic renal function monitoring in patients on target drugs, linking the laboratory to the pharmacy, assessment of the alerts by both pharmacist and GP and communication with the patient on the proposed prescription change. When implementing a PMAS, all above-mentioned steps deserve attention.

A PMAS based on renal function resulted in therapeutic advice in one of every nine target drugs in older patients on blood-glucose-lowering or cardiovascular drugs. After weighing the clinical context, the GP agreed with half of the advice. Collaboration between GP and pharmacist, using their clinical and pharmacological expertise respectively, can contribute to patient safety.

Acknowledgements

The authors would like to thank Prof. AC Egberts for his comments on the manuscript. We would very much like to thank all the pharmacists FT Schroor, FJJM van der Leemputte, DC Sietses, F Dijkhuizen-Behr, B Klok, and the general practitioners MHGA van Wijk, JJ Hammink, WJ Marée-Wibbelink, RM Linders, MP Huizing-Mientjes, MMJ Hendriks, and M van Duivenboden who participated in the study.

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7

Thirty-minute compared to standardised office blood pressure measurement in general practice

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Br J Gen Pract 2011;DOI: 10.3399/bjgp11X572427

ABSTRACT

Background Although blood pressure measurement is one of the most frequently performed measurements in clinical practice, there are concerns of its reliability. Serial, automated oscillometric blood pressure measurement has the potential to reduce measurement bias and white coat effect.

Aim To study agreement of 30-minute office blood pressure measurement (OBPM) with standardised OBPM and to compare repeatability.

Design and setting Method comparison study in two general practices in the Netherlands.

Methods Thirty-minute and standardised OBPM was carried out with the same, validated device in 83 adult patients, and the procedure was repeated after 2 weeks. During 30-minute OBPM, blood pressure was measured automatically every 3minutes, with the patient in a sitting position, alone in a quiet room. Agreement between 30-minute and standardised OBPM was assessed by Bland–Altman analysis. Repeatability of the blood pressure measurement methods after 2 weeks was expressed as the mean difference in combination with the standard deviation of difference (SDD).

Results Mean 30-minute OBPM readings were 7.6/2.5 mmHg (95% CI 6.1 to 9.1/1.5 to 3.4 mmHg) lower than standardised OBPM readings. The mean difference and SDD between repeated 30-minute OBPM's (mean difference 3/1 mmHg, 95% CI 1 to 5/0 to 2 mmHg, SDD 9.5/5.3 mmHg) were lower than those of standardised OBPM's (mean difference 6/2 mmHg, 95% CI 4 to 8/1 to 4 mmHg, SDD 10.9/6.3 mmHg).

Conclusion Thirty minute OBPM resulted in lower readings than standardised OBPM and had a better repeatability. These results suggest that 30-minute OBPM better reflects the patient's true blood pressure than standardised OBPM does.

How this fits in Office blood pressure measurement is rarely carried out according to guidelines, introducing bias in blood pressure measurements. In addition, the white coat effect contributes to unreliable blood pressure readings in up to 20% of patients. A reliable office based blood pressure measurement method that can overcome both these forms of bias is lacking. Thirty minute office blood pressure measurement appears to better reflect patient's true blood pressure status, as its readings are lower and more reproducible than those of standardised office blood pressure measurement.

INTRODUCTION

In everyday practice, blood pressure measurements are often of poor quality, mostly resulting in overestimation of the patient's blood pressure.[1] But even when performed according to the 'state of the art', blood pressure measurements in the office may not be representative of the patient's true blood pressure status because the phenomenon 'white coat effect' can introduce an additional level of bias.[2] Overestimation of blood pressure leads to overprescribing of antihypertensive drugs, with avoidable side effects and costs.

Until recently, observer bias and 'white-coat effect' could be eliminated sufficiently only with the ambulatory blood pressure measurement techniques like home blood pressure monitoring and ambulatory blood pressure monitoring (ABPM).[3;4] However, these advantages of ambulatory techniques come with a price. ABPM is not very patient- friendly[5] and is associated with disturbed sleep.[6] Home blood pressure measurements may be inaccurate because of poor measurement technique[7] and report bias.[8] These aspects make ABPM techniques less suitable for routine use in daily practice.

Serial automated blood pressure measurement , without a doctor or nurse present, also has the potential to eliminate observer bias and reduce white coat effect.[9-12] Compared to ambulatory techniques, this could be used much more easily in routine practice. The results are available during a single consultation and the procedure appears to be more patient- friendly than ABPM. In a recent study 30-minute automated blood pressure measurement (30-minute OBPM) agreed well with daytime ABPM and classified normotension, white coat hypertension, masked hypertension and sustained hypertension similarly to daytime ABPM.[13]

The aim of this study was to compare 30-minute OBPM with standardised OBPM in general practice. The level of agreement between both methods was studied the repeatability compared.

METHOD

Design

A method comparison study was performed to investigate how 30-minute OBPM agreed with standardised OBPM. As part of the method comparison, a repeatability study of 30-minute OBPM compared to standardised OBPM was carried out.[14]

Participants and setting

The study took place in two general practices of the academic practice-based research network [15] of the Radboud University Nijmegen Medical Centre. Each consecutive patient who attended the practice with a main reason for encounter that warranted blood pressure measurement was invited by the practice assistant to participate in the study. Patients gave written informed consent before participation. Exclusion criteria were atrial fibrillation, documented heart valve disease, complete axillary lymph node excision on the right side, and upper arm circumference more than 35 centimetres. Smoking, diabetes, cardiovascular disease and medication were recorded.

Blood pressure measurements

Both standardised OBPM and 30-minute OBPM were taken with the same, validated, automated oscillometric device, the Mobil-O-Graph NG (IEM GMBH, Stolberg, Germany).[16] The devices are calibrated annually. Different bladder sizes were used to match the different arm circumferences.

Two researchers (GS and SB) were trained to perform the OBPMs according to a detailed protocol (available on request) based on the recommendations of the European Society of Hypertension[17] and the American Heart Association.[18] The key elements of this protocol are listed in Boxes 1 and 2. During visit 1, standardised OBPM was carried out after a 5 minute rest period in the absence of the observer. The measurement consisted of three readings.

Immediately afterwards, 30-minute OBPM followed, consisting of 11 measurements, of which 10 were made in the absence of the researcher. The position of the patient and cuff were not altered. The result of the first measurement of both standardised and 30-minute OBPM was discarded. After two weeks the measurements were repeated by the same researcher in the same room at the same time of the day (visit 2).

To assess whether the measurement order influenced the results, an additional standardised OBPM was performed after the second 30-minute OBPM.

The last noted usual blood pressure was collected to compare with the study' standardised procedure (Table 1). The last 'usual blood pressure' was not included if there had been a medication change between this measurement and the start of the study.

Sample size

A priori a difference in blood pressure of 5 mmHg or more was deemed to be clinically relevant. To detect such a difference with a power of 90%, a significance level of 5%

Box 1 Key elements of blood pressure measurement

Key elements of standardized office blood pressure measurement	Key elements of 30 minute automated office blood pressure measurement
No talking	Same position of patient and cuff as in standardized office blood pressure measurement
Temperature in the room 22 degrees Celsius	30 seconds after standardized office blood pressure measurement
Right arm	
Placement of the cuff: 2 cm above antecubital fossa	Observer checks first measurement, then leaves the room. Patient stays in same position
Position of patient: sitting, back supported, feet flat on the floor, middle of cuff on level of right atrium	11 measurements every 3 minutes, first measurement discarded
5 minutes rest in the absence of the observer before office blood pressure measurement	
3 readings with 30 seconds in between, first reading discarded	

Box 2 Overview of study method

Time			
Retrospectively	**Usual blood pressure**		
Visit 1, T=0	Standardised OBPM: 5 minutes rest 3 measurements, First measurement discarded	30-min OBPM 11 measurements First measurement discarded	
Visit 2, T=2 weeks	Standardised OBPM	30-min OBPM	Standardised OBPM

OBPM= Office Blood Pressure Measurement

and assuming a standard deviation of the difference (SDD) of 14 mmHg, 82 patients would be needed. Considering a drop-out of 20 %, the study aimed to recruit 110 participants.

Table 1 Characteristics of subjects

Number (male/ female)	83 (32/51)
Age in years: mean (SD)	62.1 (10.7)
Mean last noted systolic blood pressure in GP record (SD) mmHg, n=78	152.8(16.5)
Mean last noted diastolic blood pressure in GP record (SD) mmHg, n=78	82.0 (10.0)
On antihypertensive drugs: number (%)	69 (83)
Smoking: number (%)	10 (12)
Cardiovascular disease: number (%)	17 (20)
Diabetes mellitus type 2: number (%)	9 (11)

Statistical methods

All data were registered and analysed in SPSS (version 16, Chicago, USA). Data were excluded for analysis if there was a change of medication type or doses between the two visits, or if fewer then 9 measurements were valid during the 30-minute OBPM.

The level of agreement between standardised OBPM and 30-minute OBPM was assessed by Bland and Altman's approach of difference-against-mean plots.[19] Because the difference increased with increasing blood pressure (positive rank correlation between the standard deviation (SD) and mean of the two blood pressure measurement methods), data were logarithmically transformed.[14] The back transformed limits of agreement were added to Bland-Altman plots on the original scale.[20] For comparison of means 95% confidence intervals(CIs) were presented For evaluation of the repeatability the mean difference was used in combination with the SDD. The repeatability of the two methods was compared by performing the Wilcoxon signed-rank test on the difference of the SD of the (logarithmically transformed) standardised OBPMs and of the SD of the 30-minute OBPMs.

RESULTS

Participants

A total of 105 patients agreed to participate in the study. Twenty-two patients were excluded from analysis: 10 because fewer than nine measurements of 30-minute OBPM were valid, six because of medication change between the two visits, two because they felt unwell during the measurements, two because they altered the

position of their arm during the measurements and two because they were unable to come for the second visit. The characteristics of included patients are shown in Table 1.

Agreement between 30-minute OBPM and standardised OBPM

Mean 30-minute OBPM readings were significantly lower than standardised OBPM readings, with a mean (absolute) difference of 7.6/2.5 mmHg (Table 2).

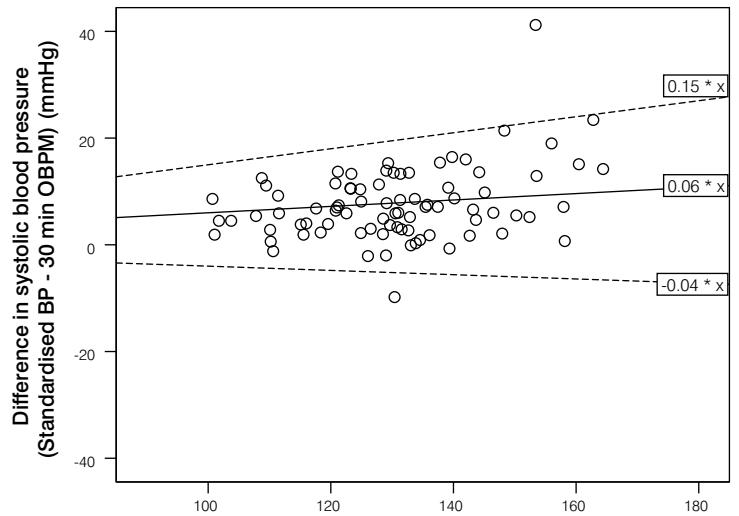
Table 2 Blood pressure results

	Mean blood pressure (SD) in mmHg		**Mean difference**
Standardized OBPM (n=83)	visit 1	visit 2	Δ ***visit 1-visit2*** (95% CI) [SDD]
Systolic	134.4 (16.4)	128.4 (14.8)	6.0 (3.6 to 8.3) [10.9]
Diastolic	84.1 (10.8)	81.8 (10.7)	2.3 (1.0 to 3.7) [6.3]
30-minute OBPM (n=83)	visit 1	visit 2	Δ ***visit 1- visit 2*** (95% CI) [SDD]
Systolic	126.8 (14.1)	123.8 (13.3)	3.0 (0.9 to 5.1)[9.5]
Diastolic	81.6 (10.1)	80.6 (10.5)	1.0 (-0.1 to 2.2) [5.3]
	Mean difference in blood pressure (95%CI)[SDD] in mmHg		
Δ ***standardized OBPM-30min OBPM*** (n=83)			
Systolic	7.6 (6.1 to 9.1) [6.8]	4.6(3.2 to 6.1) [6.7]	
Diastolic	2.5 (1.5 to 3.4) [4.5]	1.2(0.3 to 2.0) [3.7]	

OBPM=office blood pressure measurement, Δ=difference, SDD=standard deviation of the difference, SD=standard deviation, CI=confidence interval

Figure 1a and 1b shows Bland-Altman plots of systolic and diastolic blood pressures during the first visit. These plots show the differences between 30-minuteand standardised OBPM against their mean. As the difference increased with increasing blood pressure, the diverging limits of agreement were based on back transformation of results of logarithmically transformed data. The median difference in systolic blood pressure between standardised OBPM and 30-minute OBPM was 6% (95% limits of agreement ranging from -4% to 15%). The median difference in diastolic blood pressure between standardised OBPM and 30-minute OBPM was 3% (95% limits of agreement from -7% to 13%).

a



b

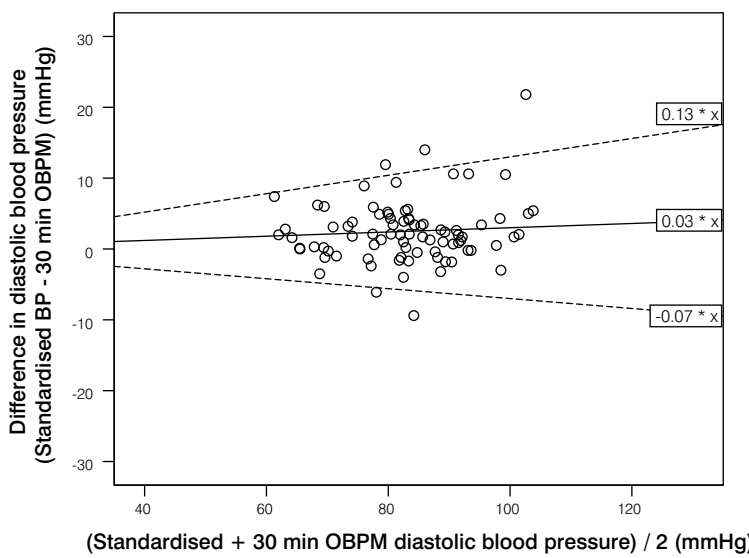
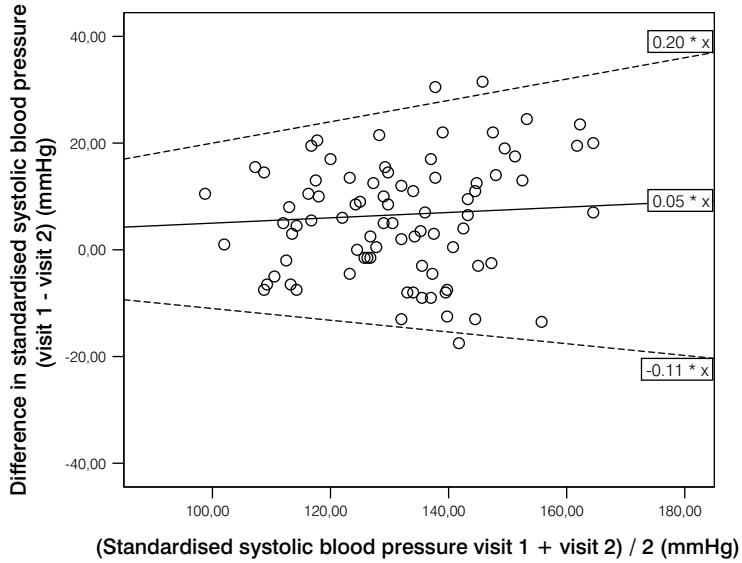


Figure 1 **a**. Comparison of systolic blood pressures. Bland and Altman plot of difference between standardised systolic office blood pressure and 30-minute systolic office blood pressure against theirmean (first visit). **b**. Comparison of diastolic blood pressure. Bland and Altman plot of difference between standardised diastolic office blood pressure and 30-minute systolic office blood pressure against theirmean (first visit).

a



b

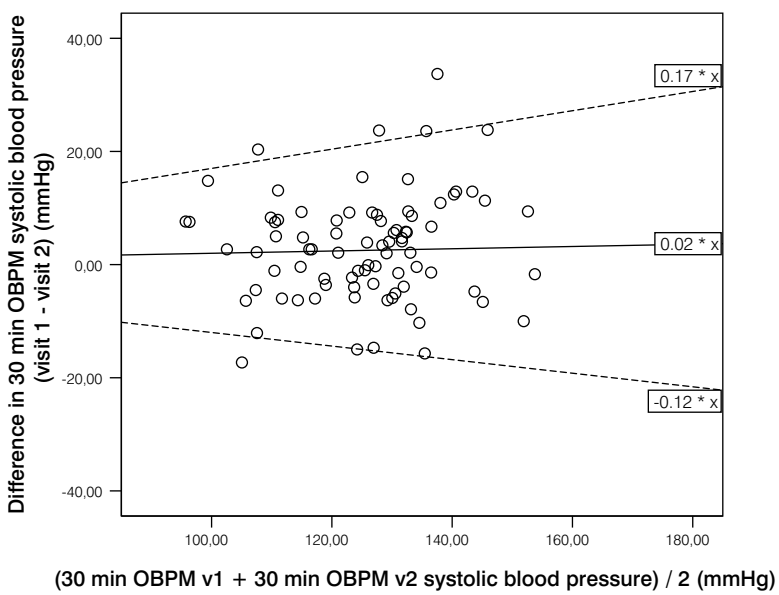


Figure 2 **a**. Repeatability of standardised OBPM. Bland and Altman plots of the repeatability of standardised systolic office blood pressure; difference between visit 1 and visit 2 against the mean. **b**. Repeatability of 30-minute OBPM. Bland and Altman plot of repeatability of 30-minute systolic office blood pressure; difference between visit 1 and 2 against mean.

Repeatability of standardised and 30-minute OBPM

Table 2 gives an overview of the data on visit 1 and 2 for both measurement methods. The mean difference between the first and second visit of 30-minute systolic OBPM is about half the mean difference of standardised OBPM. In addition, SDDs of repeat 30-minute OBPM were smaller than SDDs of repeat standardised OBPM. The Wilcoxon signed-rank test demonstrated that repeatability was significantly better for 30-minute OBPM than for standardised OBPM ($P<0.01$ for systolic and diastolic blood pressure).

Figures 2a and 2b presents Bland-Altman plots of the repeatability of systolic blood pressure for standardised and 30-minute OBPM respectively. The 95% limits of agreement are wider for standardised than for 30-minute systolic blood pressure. (for data on the repeatability of diastolic blood pressure see Table 2, a figure is available on request).

Measurement order

Comparing blood pressures measured by standardised OBPM before (128.4/81.8 mmHg) and after (128.3/82.1) the second 30-minute OBPM (visit2) demonstrated that the order of measurements did not influence the results (difference (0.1/-0.3mmHg) (95 % CI -1.6 to 1.9/-1.2 to 0.6 mmHg) [SDD 7.9/4.0 mmHg]).

DISCUSSION

Summary

In this study, mean 30-minute OBPM readings were significantly lower than standardised OBPM readings, with a difference of 7.6/2.5 mmHg. The repeatability in 2 weeks was better for 30-minute OBPM than for standardised OBPM: the difference and the SDD in both systolic and diastolic blood pressure between the two visits were significantly lower for 30-minute than for standardised OBPM.

Strengths and limitations

This study has several strengths. It was carried out in a general practice setting, where most hypertension management takes place. It is the first study to perform serial automated OBPM (AOBPM) in general practice, with a common 24-hour ambulatory device. The advantage is that many practices already own one of these devices, and they are likely to be standard equipment in all general practices in the near future. With one type of device (and consequently just one type of software), practices can then run both office and ambulatory measurement protocols. The presentation of data on repeatability is of additive value in judging serial AOBPM in the office.

This study did not randomise the measurement order, which would have been methodologically more accurate. To study whether any time effect would bias the results, a second standardised OBPM was added after 30-minute OBPM. Standardised office blood pressure before and after 30-minute OBPM did not differ, so randomisation of measurements appear to have had no significant effect on the results. By introducing 30-minute OBPM, the study aimed to reduce the 'white-coat effect' by leaving the patient alone in a room. The practice setting, which is also part of the 'white-coat effect', may still contribute to a blood pressure rise.

Thirty-minute OBPM takes less time from a healthcare professional than the 8–12minutes required for a standardised OBPM.[1] However, it takes organisational skills and a spare room to implement 30- minute OBPM in daily practice. Previous research suggests that a duration of 30minutes may not be necessary. [13] A shorter measurement time may help to overcome organisational problems.

Results were presented both absolutely and relatively. The data in Table 2 were presented in absolute figures. However, it is important to realise that the presented results depend on the height of the blood pressure. Therefore, a relative measure is, strictly speaking, more appropriate. Most data were analysed in this relative form (after log transformation) as can be seen in the Bland–Altman plots, but to facilitate interpretation and enable comparison with other studies, absolute figures are presented in Table 2.

Comparison with existing literature

The study data support abundant evidence on the difference between usual blood pressure measurement and standardised OBPM based on measurement bias.[1,21] In real life, the difference between office blood pressure measurement and 30-minute OBPM will be greater than the difference found in this study, as lack of measurement technique in daily practice will lead to higher blood pressure results.

The mean last noted usual systolic blood pressure was 18mmHg higher than standardised OBPM (Tables 1 and 2). With the choice to compare 30-minute OBPM with standardised OBPM measurement, bias was eliminated as potential (confounding) cause for a difference in blood pressure. It is therefore hypothesised that the presented difference in blood pressure is a result of the reduction of the 'white-coat effect' with 30-minute OBPM. The fact that standardised OBPMs before and after 30-minute OBPM were the same, underlines that a fall in blood pressure during 30-minute OBPM is influenced by the absence of the healthcare professional (and, less so, caused by a long rest period or regression to the mean). Other studies also demonstrated that repeated automated measurements with the patient alone in

an examining room give lower results than standardised measurements. Recently, Myers et al found a difference of 5.4/2.1mmHg between automated office blood pressure and conventional manual office blood pressure.[22] These findings, which point in the same direction of lower results of automated measurements, are interesting, as their approach differed from the present one in two aspects: the researchers followed a shorter measurement procedure (10 minutes) and they used routine — not standardised — OBPM as the reference. It would be valuable to establish the repeatability of Myers et al's short procedure. Considering the wide limits of agreement in relation to awake ambulatory blood pressure (limits of agreement –31.9 to 36.6mmHg,[22] where 30-minute OBPM compared to daytime ambulatory blood pressure revealed limits of –19 to 19mmHg[13]), one may assume that the repeatability of their short procedure will not be as good as the present longer procedure.

The differences between automated measurements with the patient alone in an examining room and standardised measurements seem to depend on the baseline blood pressure level of the study population; mean automated blood pressure was 142/80mmHg in an outpatient clinic population (difference 20/5mmHg)[10] and 115/71mmHg in an open population study (difference 3/3mmHg).[23] The mean automated blood pressure of the present study population (134/84mmHg) was intermediate compared to the abovementioned studies, with the differences also intermediate. This is in line with the observation in the present study that differences are related to blood pressure level (Figures 1a and b).

To the authors' knowledge, data on the repeatability of any serial AOBPM were lacking until now. This is unfortunate because study of repeatability should be part of every validation procedure.[14] The relevance of repeatability was underlined recently by Palatini et al, who reported that ABPM only predicted end-organ damage in subjects with reproducible recordings.[24]

In the absence of data on the repeatability of serial AOBPM, data in the present study were compared with reproducibility studies of 24-hour ABPM. In a study in 508 hypertensive patients,[24] the SDD of 24-hour ABPM was 8.3/6.4mmHg. Stergiou et al reported an SDD of 8.3/5.6mmHg for 24-hour ABPM; the SDD of the awake 24-hour ABPM was 10.0/6.6.[25] In this last-mentioned article, the SDD for clinic blood pressure measurement was 11.0/6.6mmHg,[25] comparable to the SDD reported in the present study for standardised OBPM (10.9/6.3mmHg).This study revealed that 30-minute OBPM had a good repeatability, as the difference between visits 1 and 2 was less than 5mmHg and the SDD (9.5/5.3mmHg) was in agreement with above-mentioned studies concerning the repeatability of 24- hour ABPM.

Implications for practice and research

The results of this study demonstrate the potential of 30-minute OBPM to reduce measurement bias and 'white-coat effect' in the office, without the need for ambulatory techniques. Combined with the authors' previous work, a 30-minute OBPM is suggested to be a valid, office-based alternative to daytime ABPM or home blood pressure measurement, in attempting to determine one's true blood pressure status. Meanwhile, the authors realise that 30-minute OBPM cannot replace several relevant features that are unique for 24-hour ABPM, like measurement of blood pressure variability and nighttime blood pressure.

Myers has already suggested how to implement the use of serial AOBPM in daily practice.[26] He advocates using the same reference value for the diagnosis of hypertension as in home blood pressure monitoring or daytime ABPM(135/85mmHg). The author's previous finding that 30-minute OBPM outcome agreed well with daytime values of ABPM supports our proposal.[13]

Further research should focus on the comparison of serial AOBPM with home blood pressure measurement and on the optimal measurement duration. In addition, implementation studies on cost effectiveness are required.

In conclusion, 30-minute office blood pressure measurement resulted in lower readings than standardised office blood pressure measurement and had a better repeatability. The favourable repeatability and the lower values of 30-minute OBPM are promising for its value in blood pressure management in general practice.

Acknowledgements

We would like to thank the doctors, nurse practitioners, assistants, and patients of the general practices in Berghem and Schaijk (The Netherlands) for their cooperation.

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7a

Comparing Blood Pressure Measurement Methods: Differences Depend on Blood Pressure Height

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Hypertension 2010;56;e4; 3 May 3, 2010 letter to editor

We welcomed the article from Myers et al[1] on automated office blood pressure (AOBP) measurement. It is well known that the differences between routine blood pressure (BP) measurements taken by health professionals in daily practice and BP measurements taken by well-trained observers within the framework of scientific studies are impressive. Because of this, routine BP measurement is of limited value. The studies on AOBP open the way in realizing a valid BP measurement in the office. We would like to add a few comments on the data presentation and on the proposed algorithm.

Differences in BP readings between different measurement methods are strongly dependent on the population in which BP measurements are taken. A high mean difference of 20/5 mm Hg between standardized automated measurements and automated measurements with the patient alone in a room was found in patients referred to a specialist for hypertension treatment. A low difference of 3/3 mm Hg was found in an open population. The mean automated BP was 142/80 mm Hg in the first mentioned study by Myers[2] and 115/71 mm Hg in the open population study.[3] In the recent article by Myers et al,[1] Bland-Altman plots show the differences between manual office BP measurement and the daytime ambulatory BP against their mean (Figure 1A in Reference 1) . As one can see in the plots, the differences tend to 0 at normal BP levels and increase with increasing BP, the so-called positive rank correlation. So there is a proportional error indicating that the differences are not normally distributed. Therefore, the data need to be logarithmically transformed to specify the limits of agreement. After back transformation of the data, limits of agreement are percentage-plotted in the original scale. The median difference in systolic BP between office BP measurement and awake ambulatory BP measurement against their mean is then presented as a relative difference (a percentage).[4]

Considering the fact that the difference between manual office BP and awake ambulatory systolic BP tends to 0 in patients with normotension, we only advise an AOBP for those with an elevated routine BP. This would mean that AOBP is not mandatory for every BP measurement but only in case of a manual office BP >140/90 mm Hg.

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8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

The aim of this thesis was to explore current management of patients with Chronic Kidney Disease (CKD) in primary care and to evaluate shared care models that should facilitate optimal treatment in the patients' own environment. In the previous chapters we presented the results of the individual studies. In this last chapter the findings will be summarised and discussed. Furthermore, we will outline implications for daily practice and future research.

MAIN FINDINGS

1. Prevalence of patients with chronic kidney disease in primary care

We studied a primary care database of 207,469 patients. Data on kidney function or albuminuria were known in 64,102 patients. 9295 patients met the criteria for CKD stages 1 to 5 as defined by the KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines, resulting in a prevalence of patients with CKD of 5.7% **(chapter two)**. In our study KDOQI stages 1 to 2 accounted for 1.05% and stages 3 to 5 for 4.66%.

2. Quality of care for patients with CKD in primary care related to the guideline advice

Evidence based guidance aims to improve quality of CKD care. In the Netherlands, the interdisciplinary CKD-guideline for primary care and nephrology serves this purpose.[1] This guideline has many similarities to the CKD-guideline from the National Institute for Health and Clinical Excellence (NICE) in the UK.[2] Quality of care can be judged by the following components: a)monitoring of disease progression (kidney function, albuminuria, blood pressure); b)monitoring of renal metabolic parameters; c)recognition of CKD by coding the diagnosis on the episode list in the electronic medical record and d)achieving blood pressure targets. In **chapter two** we described the results of a study which evaluated these quality of care aspects in a retrospective analysis of the data of 8845 patients with CKD over a period of 15 months prior to data extraction. Patients under nephrology care were not included.

a) Monitoring of disease progression was performed according to the guideline recommendations in 43% of the CKD patients;
b) Monitoring of metabolic parameters was complete in only 2% of the patients where it was indicated;
c) Recognition of CKD: 32% of the CKD patients had CKD documented on the episode list in the electronic patient file as ICPC code. For CKD stages 1 to 2 and 3 to 5 ICPC-coding was 4% and 34% respectively;

d) Blood pressure was below 140/90 mmHg in 44% of the patients.

Characteristics related to high quality of care were diabetes, and to a lesser extent hypertension, male sex and rural practice location. We concluded that there is room for improvement in all quality of care aspects for CKD patients in primary care.

3. Prevalence of renal metabolic abnormalities in patients with CKD in primary care

Currently, bone and mineral disorders are considered an important constituent of CKD. Monitoring of these abnormalities occurs infrequently in primary care and this was confirmed in our study on quality of care **(chapter two)**.[3] We used patient data from a randomised study to assess abnormalities in PTH, calcium, and phosphate levels. A total number of 174 patients in primary care was included **(chapter three)**. Mean eGFR was 50.3 ml/min/1.73 m^2. Calcium and phosphate abnormalities were infrequent. In contrast, elevated PTH levels occurred very often: in 40% of the patients PTH levels were above normal. We determined risk factors for abnormal PTH-levels by stepwise logistic regression. eGFR, heart failure and triglycerides contributed to elevated PTH, but their predictive value was very limited (partial R-square 13.5%, 6.0% and 2.0% respectively).

4. Would a shared care model between nurse practitioner, general practitioner and nephrologist, supported by a web-based consultation system (Telenephrology), contribute to the quality of care for patients with chronic kidney disease?

Organising care for patients with CKD, who often have many co-morbid conditions, is challenging. A shared care model between general practitioner, nurse practitioner and a nephrology team could improve quality of care and outcomes in patients with CKD.[4] In the SHARING study (SHARed care for patients with chronic kidney disease In Nephrology and General practice) we assessed the effect of a shared care model on blood pressure, on kidney disease measures, on use of lipid lowering drugs or renin-angiotensin system inhibitors and on functional health status **(chapter four)**. In a cluster randomised controlled trial in the Netherlands five primary care practices were allocated to the shared care model and four practices to usual care during one year. The multifaceted model consisted of training of professionals, structured care by a nurse practitioner in primary care and the opportunity to consult a nephrology team in a protected digital environment (Telenephrology). 164 patients with diabetes mellitus type 2 and/or hypertension with an estimated GFR $<$ 60 ml/min/1.73 m^2 were included for analysis. Main outcome measures were lowering of blood pressure and the achievement of blood pressure targets (130/80 mmHg). Secondary outcome measures were laboratory parameters and functional health status.

BP after one year was 134.7/73.8 mmHg in the intervention group and 142.9/80.9 mmHg in the control group (difference systolic: 8.2 mmHg, 95%CI 3.6 to 12.9 mmHg; diastolic: 4.7mmHg, 95%CI 1.1 to 8.4 mmHg). Blood pressure decreased with 8.1 (95% CI 4.8 to 11.3) /1.1 (95% CI -1.0 to 3.2) mmHg in the intervention group compared to -0.2 (95% CI -3.8 to 3.6)/-0.5 (95% CI -2.9 to 1.8)mmHg in the control group. Achievement of systolic and diastolic blood pressure targets was 44%/71% in the intervention group versus 22%/50% in the control group ($p= 0.003/0.007$). The improvement in blood pressure control was paralleled with an increase in the use of renin-angiotensin system inhibitors (73% versus 51%)($p=0.01$). PTH was 6.1 pmol/l in the intervention group and 8.2 pmol/l in the control group ($p=0.02$). This was in parallel with the more frequent use of vitamin D, which was 15% and 1% respectively. Other kidney disease measures did not show clinically relevant differences between the intervention and the control group. Cholesterol and LDL levels decreased in the intervention group during the intervention from 4.9 to 4.6 mmol/l and from 2.9 to 2.5 mmol/l respectively ($p<0.001$ and $p<0.001$). This was in parallel with an increase in the use of lipid lowering drugs from 59% to 73% ($p<0.001$).

Since blood pressure is the most important modifiable risk factor for disease progression and outcome in CKD patients, we concluded that a shared care model seems beneficial in patients with CKD in primary care.

5. Feasibility of a web-based consultation between general practitioner and nephrologist

During the SHARING study we developed a web-based consultation system: Telenephrology. With this system, relevant data are exported from the electronic patient file to a protected digital environment from which advice can be formulated by the nephrologist. In **chapter five** we described the results of an observational, prospective study in which we analysed Telenephrology-consultations by 28 general practices and five nephrology departments. The primary outcome was the potential reduction in in-person referrals, measured as the difference between the number of intended referrals as stated by the general practitioner and the number of referrals requested by the nephrologist. 122 new consultations were included. In the absence of Telenephrology 43 patients (35.3%) would have been referred by their general practitioners, whereas the nephrologist considered referral necessary in only 17 patients (13.9%) ($p<0.001$). The general practitioner would have treated 79 patients in primary care. In ten of these patients the nephrologist deemed referral necessary.

We concluded that a web-based consultation system could reduce the number of referrals. In that way Telenephrology may contribute to an effective use of health facilities by allowing patients to be treated in primary care with remote support by a

nephrologist. The system was feasible, since it was mainly used during office hours and mean consultation time was only nine minutes.

6. How could general practitioners and pharmacists contribute to medication safety in patients with CKD and diabetes or hypertension?

The prescription of potentially harmful drugs is a threat for CKD patients: impaired renal function leads to increased serum drug levels in drugs that depend on renal excretion, drugs that can be directly nephrotoxic or that can indirectly damage the kidney by affecting renal perfusion. Collaboration between general practitioner and community pharmacist may contribute in finding and reducing medication errors. In **chapter six** we described a pharmacy medication alert system based on renal function. This system resulted in therapeutic advice with respect to dosage of discontinuation in one of every nine prescriptions of target drugs in elderly patients using blood-glucose lowering or cardiovascular drugs. Taking the clinical context into account, the general practitioner agreed with the advice half the time. Overall, the general practitioner agreed to rectify the prescription in 5% of the cases. The drugs most frequently involved were diuretics (41.3% of therapeutic advice), blood glucose-lowering drugs (14.0%), digoxin (11.2%), and renin-angiotensin system inhibitors (10.5%). We concluded that collaboration between general practitioner and pharmacist, using their clinical and pharmacological expertise respectively, can contribute to patient safety.

7. Validation study

As blood pressure is related to cardiovascular and renal outcome in patients with CKD, adequate measurement of blood pressure is essential in directing treatment decisions. We validated a 30-minute automated blood pressure measurement (30-min AOBPM) in primary care (**chapter seven**). This measurement method resulted in lower readings than standardised office blood pressure measurement and had a better repeatability. 30-min AOBPM may be of value in the diagnosis and treatment of hypertension, but prognostic studies on the relation between 30-min AOBPM measurement results and cardiovascular outcome are needed to validate the clinical value.

DISCUSSION

CKD and its complications have, beside the personal impact, a high impact on organisational and economic systems.[5] With an ageing population and increasing prevalence of diabetes and hypertension, the prevalence of CKD has risen to 13% in 2004 in the USA and 10% in the Netherlands.[6,7] Patients with CKD are at risk for both renal and cardiovascular morbidity. The increased cardiovascular risk in CKD patients is a major concern and leads to a high burden of adverse outcomes.[8,9] This, added to the fact that patients with CKD often suffer from other chronic conditions, makes management complex.[10,11] In the primary care setting CKD is characteristically associated with hypertension or diabetes and a predominant occurrence in the elderly. It is only since the last decade that the potential adverse outcomes of CKD may count on awareness in primary care. The international classification of CKD and the default reporting of estimated glomerular filtration rates (eGFR) have contributed to this awareness.[12] Furthermore, the recommendations for regular serum creatinine measurements in high-risk groups have led to a high proportion of patients with diabetes and hypertension who have their renal function checked on a regular basis.

The high prevalence of recognised CKD patients not only brings along a burden of disease but also a burden of treatment. Management of CKD should preferably take place in primary care, while secondary care facilities should be used when needed.[13,14] The engagement of primary care in CKD management can lead to an increase in quality of care in relation to evidence-based guidance.[15] This will not only be cost-effective, but also is more convenient for the patient. In our studies we identified possibilities to improve care at the primary-secondary care interface: the delegation of tasks to a nurse practitioner, web-based consultation of a nephrology team and collaboration between general practice and pharmacy. We will discuss our findings in the light of what was already known on CKD management in primary care. Then we will discuss the hurdles that need to be taken to optimise CKD management in primary care, followed by recommendations for daily practice and for further research.

Findings in the light of prior knowledge

Prevalence

We found a prevalence of known CKD patients of 5.7%. A population study in the Netherlands showed that the community prevalence of CKD is 10.4%, with 5.1% in CKD stage 1-2 (predominantly defined by the presence of micro-albuminuria), and 5.3% in CKD stage 3-5 (eGFR $<$ 60ml/min/1.73m^2 with or without albuminuria). [7] In our study KDOQI stages 1 – 2 accounted for 1.05% (21% of the population prevalence) and stages 3 – 5 for 4.66% (88% of the population prevalence). These data clearly reflect current guidelines, which do not support routine testing for micro-albuminuria. Most

importantly, and relevant in view of the debate on the need for CKD-screening programs, almost 90% of patients with CKD and impaired renal function could be identified by searching primary care records.

Quality of care

With respect to quality of care, the performance on monitoring of disease progression was similar to other studies in primary care.[16,17] Monitoring of metabolic abnormalities in our study was very low: PTH was monitored in 4% of the patients where it was indicated versus 13% in an American study.[17] The follow-up of albumin creatinine ratio and blood pressure in our study was much lower than the 82% for urine albumin creatinine ratio and 98% for blood pressure readings that were found in the United Kingdom in 2010/2011.[18]

The blood pressure target of 140/90 mmHg was met in 44% of the patients, which is comparable to other studies. Italian researchers found that 44% of CKD patients in primary care had a blood pressure <140/90 mm Hg and in other studies a lower target of 130/80 was met in 27% to 54% of the patients. [19-21]

Recognition (ICPC-coding on the episode list in the electronic medical record) is much more than an administrative issue: improved recognition appeared to be related with a better quality of care.[19,21]. When it comes to recognition results vary enormously between studies: recognition varied between 2.4% and 24 % in routine practice and increased to 70% after introduction of a quality improvement program.[17,19,22-24] National or local agreements may well be the reason for this wide variation. In the United Kingdom, the introduction of the Quality of Outcome Framework, in combination with pay for performance, has led to a rise in quality of care in all aspects.[15,18,25]

All in all, quality of CKD care in daily general practice in the Netherlands offers room for improvement. One should realise that our data originated from the year following introduction of the interdisciplinary CKD-guideline for primary care and nephrology. It may well be that a few years later targets will be better met. It will be interesting to see whether the Telenephrology intervention in the CONTACT study (Consultation Of Nephrology by Telenephrology Allows optimal Chronic kidney disease Treatment in primary care, final results due in 2013) leads to better quality of care. Preliminary results suggest that the mere focus on CKD, by providing lists of patients that met CKD criteria, improved quality of care even in the control group.[26]

Metabolic abnormalities

Elevated PTH levels are associated with adverse cardiovascular outcomes in patients with CKD.[27-29]. Elevated PTH-levels occur in earlier stages of CKD than generally is expected.[30-32] Studies on PTH have been mainly performed in secondary care. Data on prevalence of metabolic abnormalities in patients that are under care of their general practitioner are rare. In our study PTH levels were above normal in 40% of patients with known chronic kidney disease and diabetes or hypertension. This was in line with what was found in a study in out-patient clinics.[33] Guidelines vary in their recommendations on testing for metabolic abnormalities. The NICE guideline advises measurement of PTH, calcium and phosphate in patients with eGFR < 30 ml/min/1.73 m^2.[2] The KDOQI and KDIGO guidelines recommend these measurements in patients with eGFR < 60 ml/min/1.73 m^2.[12,34] This difference can be traced to the lack of evidence on the effect of PTH lowering on cardiovascular outcomes in primary care. Awaiting further evidence, we suggest that general practitioners test patients with CKD stage 3 or worse on PTH, calcium and phosphate as advised in the KDIGO and KDOQI guidelines. We may not that elevated PTH levels could be a reflection of vitamin D deficiency, which is frequent in the elderly.

As vitamin D treatment is cheap and safe, GPs could consider prescribing vitamin D in patients with elevated PTH levels.

Shared care

The call for shared care in managing CKD is not new. Many initiatives in that direction have been described with predominantly positive results.[4,14,35,36] However, firm evidence of the efficacy of such an approach based on data from cluster randomised controlled trials was not available.[37] The QICKD study, a cluster randomised trial that compares several quality improvement interventions to lower systolic blood pressure in CKD patients in primary care, will hopefully provide further evidence on quality improvement strategies.

Our SHARING trial has provided strong encouragement to embed primary care CKD management in an organisation model which includes nurse practitioner and nephrologist. We noted, though, that our results were weakened somewhat by a high value for the intra-cluster correlation coefficient.

Telenephrology

We evaluated the implementation of Telenephrology and the potential of reducing referrals. Some other studies focused on improvement of the referral process in CKD patients. For example, a system of continuous education, (email)consultations and shared clinical information in Barcelona led to more adequate and better prioritised

referrals. [38] In Hawaii nephrologists went a step further: they evaluated electronic patient records on population level and gave unsolicited advice to general practitioners on referral and patient management. This led to an increase of timely referrals for renal replacement therapy and a reduction in low-risk referrals.[39] In the United Kingdom electronic sharing of primary care electronic patient records led to a reduction of paper referrals but it was not clear whether the total number of referrals changed.[40]

Our Telenephrology system was unique in the sense that only relevant information was presented in a protected digital environment and that the communication was embedded in the electronic patient record. The CONTACT study (Consultation Of Nephrology by Telenephrology Allows optimal Chronic kidney disease Treatment in primary care) will evaluate the effect of Telenephrology on referrals and quality of care in a cluster randomised controlled trial.

Teleconsultation is a very promising instrument to dissiminate secondary care knowledge to primary care. Application of Teledermatology for example, proved to realise higher quality of care at a lower cost. [41] The high demands on health care from an ageing population with many chronic conditions, ask for creative innovations in the primary-secondary care interface. Telenephrology can well be one of these.

Shared care with pharmacist

Evaluation of medication errors in relation to renal function (HARM study: Hospital Admissions Related to Medication) teaches us that in the patient group monitored by general practitioners, renal function was available but the proper actions were undertaken less often than in the hospital monitored group. This may have been the result of general practitioners' lack of knowledge on the appropriate actions. [42] This underlines our aim to involve pharmacists in preventing medication errors in relation to renal function. Our study showed implementation of a pharmacy medication alert system led of rectification by the general practitioner in 5% of prescriptions in high-risk patients. In Germany, a multifaceted intervention including the use of a software program reduced the number of prescriptions that exceeded the maximum recommended standard daily doses in relation to renal function.[43]

Quality improvement strategies between pharmacist and general practitioner can be (cost) effective, but are also labour intensive.[44-47] Focusing on high risk patients, sensibly using information technology and linking of laboratory to pharmacy can contribute to an efficient way of working.[48]

Innovative aspects of this study:

- Monitoring of disease progression and recognition of CKD is suboptimal
- Monitoring of eGFR and albuminuria is better in patients with diabetes than in patients without diabetes
- Monitoring of metabolic disturbances is far below the guideline advice
- Elevated PTH-levels are highly prevalent in patients with CKD and diabetes or hypertension in general practice
- Blood pressure targets are often not met
- Shared care between general practice and nephrology is beneficial in reducing blood pressure
- Telenephrology is a feasible instrument to disseminate secondary care nephrology knowledge to primary care and to optimise referrals
- A pharmacy medication alert system can contribute to a reduction in medication errors

Hurdles

In our studies we identified the following hurdles that need to be cleared to bring CKD management in primary care in accordance with the prevailing guidance:

1. Recognition of CKD was poor. Although routine primary care laboratory data identified the majority of patients with CKD stage 3 to 5, only one third of these patients had an ICPC code of CKD on the diagnosis list. This does not necessarily mean that un-coded CKD patients do not receive adequate follow-up and treatment, but it certainly implies that prescribing alerts regarding renal function will not be generated.
2. Quality of care regarding adequate follow-up was suboptimal: the number of CKD patients that had a record of a urine albumin creatinine ratio in the previous 15 months was only 48%. Also, the number of CKD patients that had blood pressure readings in the previous 15 months was 73%, which was lower than has been observed in structured diabetes care in the Netherlands (99%).[49]
3. Although the prevalence of elevated serum parathyroid hormone (PTH) levels in primary care is high, testing of metabolic parameters was very low.
4. Blood pressure targets were not well met.
5. Only 54 % of patients that should have been referred according to the prevailing guideline were actually referred (there might have been good reasons for this).
6. Safe prescribing in relation to renal function was not a reality yet. It was remarkable that data on renal function were available in many patients (more frequently in patients with diabetes than in patients with hypertension), but appropriate action was often not taken.

Recommendations for daily practice

The previously mentioned hurdles lead to suggestions for improvement:

1. Feedback to general practices, based on laboratory findings in the electronic patient record, could be an effective way to help practices improve their recognition of CKD patients.[50,51]
2. To improve follow-up, nurse practitioners can contribute to quality of care by performing regular patient evaluations (chapter 4). This can well be integrated in the current diabetes and hypertension schemes in general practice that are run by nurse practitioners. Incentives to promote structured follow-up could be of help.
3. Follow-up of metabolic abnormalities could be improved by educating general practitioners and by providing feedback on data extracted from the electronic patient record. Our research showed that shared care, supported by Tele-nephrology consultations, will also be of help in focussing attention on mineral and bone metabolism (chapter 5). Clinical decision support systems have shown to be of benefit. [52,53] More fundamental, the lack of evidence on the effect of PTH lowering on cardiovascular outcome should be addressed first of all.
4. Blood pressure targets in CKD management require more awareness in primary care. General practitioners have less confidence in treating CKD than in treating diabetes and hypertension. This is reflected in a lower achievement of targets.[54] On the other hand, too much lowering of blood pressure is associated with stroke and increased mortality in frail elderly.[55,56] Additive markers for overtreatment are needed. [57] Shared care could contribute to titration of blood pressure lowering (chapter 4). Furthermore adequate blood pressure measurement requires attention. [58] Home blood pressure measurements (self monitoring or 24 –hour ABPM) and 30-minute automated measurement in the office provide validated blood pressure measurement techniques (chapter 7). Further implementation of these techniques and adequate reporting in primary care computer records is advisable.
5. The low referral rate in patients in whom referral was indicated (chapter 2) could partly be due to a lack of recognition, severe co-morbidity or to scepticism regarding the guideline advice. The fact that impaired renal function is highly prevalent in elderly people and renal prognosis and mortality are often not affected, may make it difficult to distinguish which patients are at risk.[59] Easily accessible consultation of a nephrology team to discuss necessity of referral will be of added value.
6. To optimise drug prescribing in patients with decreased renal function, many steps need to be taken: systematic renal function monitoring in patients on target drugs and registering a diagnostic code for impaired renal function to activate the prescribing alert system. Furthermore, in unstable clinical situations like dehydration, renal function needs to be re-evaluated. Electronic alert systems in general practices are sophisticated, but alerts are often ignored.[60] Further steps

to optimise drug prescribing should include linking laboratory to pharmacy, assessment of the alerts by the pharmacist, discussion of the advice with the general practitioner to consider the individual clinical context and communication with the patient on the proposed prescription change.

RECOMMENDATIONS FOR FUTURE RESEARCH

In the field of CKD management at the primary-secondary care interface a lot has been achieved in the past decade. Areas of uncertainty remain. This brings us to the following recommendations for future research:

- Study patient preferences on treatment environment and explore possibilities for improved self-management.
- Perform qualitative studies on general practitioners views on CKD treatment goals and referral.
- Identify which elderly patients with CKD in primary care are at high risk of poor outcomes, so that care can be focused.
- Study the effect of PTH lowering in primary care patients on cardiovascular outcome.
- Explore possibilities for discharge from secondary care to primary care, supported by web-based consultation.[61,62]

Future studies should contribute to the primary care strength of focusing on patients that will benefit from our interventions, without labeling each abnormal laboratory result as an illness.

CONCLUSIONS

In the field of Chronic Kidney Disease many players have a role: amongst others, patient, nurse practitioner, general practitioner, pharmacist and nephrologist need well defined tasks and responsibilities. Not only evidence-based guidance, but also implementation tools that address practical and mental barriers are required to let the players optimally perform their roles. In the collaboration between players a world can be gained when shared care is the starting point and communication is facilitated by information technology. The result could be that optimal treatment is realised in cooperation with the patient in his or her own environment.

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SAMENVATTING

Chronische nierschade (CNS) en de complicaties daarvan, veroorzaken, naast de grote persoonlijke impact, veel druk op gezondheidszorg voorzieningen. Door de vergrijzing en de toename van suikerziekte en hoge bloeddruk is de verwachting dat CNS in de toekomst nog meer zal vóórkomen dan het al doet. Patiënten met CNS hebben een verhoogd risico op het ontwikkelen van hart- en vaatziekten. Bovendien hebben zij vaak nog andere chronische aandoeningen. Dat maakt dat een groot aantal behandelaars bij de patiënt is betrokken. Voornoemde facetten (chronische ziekte, veel bijkomende ziekten, veel behandelaars) maken de organisatie van zorg rond deze patiënten groep complex. Bij voorkeur vindt de zorg plaats in de eerste lijn. Verwijzing naar de tweede lijn dient alleen plaats te vinden waar nodig.

Het doel van dit proefschrift was om het management van CNS in de eerste lijn in kaart te brengen en om te onderzoeken of een model van gedeelde zorg kan bijdragen aan optimale zorg in de eigen omgeving van de patiënt. In dit hoofdstuk zal ik de bevindingen samen vatten en een paar aspecten uit de discussie van het proefschrift naar voren halen.

BELANGRIJKSTE BEVINDINGEN

1. Vóórkomen van CNS in de eerste lijn

Wij onderzochten gegevens van ruim 200.000 patiënten uit 47 huisartspraktijken. Bij 64.102 van hen was informatie over de nierfunctie of de eiwituitscheiding in de urine bekend. 9295 patiënten voldeden aan de internationale diagnose criteria voor CNS, wat betekent dat bij 5.7% van de patiënten in de huisartspraktijk laboratorium gegevens wijzen op het bestaan van CNS **(hoofdstuk 2).**

2. Kwaliteit van zorg voor patiënten met CNS in de eerstelijn vergeleken met de richtlijnen

Richtlijnen beogen de kwaliteit van zorg voor CNS patiënten te verbeteren. In Nederland geeft de Landelijke Transmurale Afspraak CNS adviezen voor diagnostiek en behandeling in de eerste lijn en voor afstemming van zorg met de tweede lijn. Wij onderzochten of de kwaliteit van zorg overeenkomt met de richtlijn. Daartoe splitsten wij de kwaliteit van zorg in de volgende componenten: a) monitoren van ziekte progressie (onderzoek van nierfunctie, eiwit uitscheiding, bloeddruk); b)monitoren van zogenaamde metabole parameters; c)herkennen van CNS door de ziekte te coderen in de probleemlijst van het elektronisch patiënten dossier, en d)het bereiken van bloeddruk doelen. We onderzochten bij 8845 patiënten met CNS in hoeverre de zorg in de voorafgaande 15 maanden voldeed aan de richtlijn. **(hoofdstuk 2)**

a) Onderzoek naar nierfunctie en eiwituitscheiding was uitgevoerd bij respectievelijk 82% en 48% van de CNS-patiënten. De bloeddruk was bij 73% van de patiënten gemeten. Bij 43% van de patiënten was de voortgang van de ziekte gecontroleerd volgens de richtlijn.
b) Slechts bij 2% van de patiënten waar het volgens de richtlijn had moeten gebeuren waren de metabole parameters gecontroleerd.
c) 32% van de CNS patiënten had CNS gedocumenteerd als code in de probleem lijst van het elektronisch patiëntendossier.
d) Bloeddruk was onder de 140/90 mmHg bij 44% van de patiënten.

Factoren gerelateerd aan hoge kwaliteit van zorg waren het bestaan van diabetes en, in mindere mate, hoge bloeddruk, mannelijk geslacht en het feit dat de praktijk zich op het platteland bevond. We concludeerden dat er ruimte voor verbetering is in alle aspecten van kwaliteit van zorg voor CNS patiënten in de eerste lijn.

3. Vóórkomen van metabole stoornissen bij patiënten met CNS in de eerste lijn

Problemen in de botombouw worden tegenwoordig als een belangrijke factor bij CNS beschouwd omdat deze problemen samen hangen met het verhoogde risico op hart- en vaatziekten bij CNS patiënten. Door middel van bepaling van calcium-, fosfaat- en PTH spiegels kunnen deze zogenaamde metabole stoornissen in de gaten gehouden worden. Dit gebeurt nog weinig in de eerste lijn. Dit zagen we bevestigd in ons onderzoek naar kwaliteit van zorg. In een ander onderzoek (de Sharing studie, waarover later meer) beschikten wij over calcium, fosfaat en PTH gegevens van 174 patiënten **(hoofdstuk 3)**. Dit stelde ons in de gelegenheid te onderzoeken hoe vaak metabole stoornissen voor komen in de eerste lijn. Calcium en fosfaat verstoringen waren zeldzaam. Verhoogde PTH spiegels daarentegen kwamen veel voor: bij 40% van de patiënten waren de PTH spiegels hoger dan de normaal waarde. We stelden voorspellende factoren vast voor een verhoogd PTH. De nierfunctie, hartfalen en triglyceriden droegen bij aan een verhoogd PTH, maar hun voorspellende waarde was zeer beperkt.

4. Zou een model van gedeelde zorg tussen praktijkondersteuner, huisarts en nefroloog, met ondersteuning van een webbased consultatie systeem (telenefrologie) kunnen bijdragen aan de kwaliteit van zorg voor patiënten met CNS?

Het is een uitdaging om de zorg voor patiënten met CNS, die vaak een aantal chronische aandoeningen tegelijkertijd hebben, goed te organiseren. Een model van gedeelde zorg tussen huisarts, praktijkondersteuner en nefroloog zou de kwaliteit van zorg en de uitkomsten kunnen verbeteren. In de SHARING studie (SHARed care for patients with chronic kidney disease In Nephrology and General practice) hebben

we onderzocht wat het effect van een dergelijk model was op de bloeddruk, nierfunctie waarden, gebruik van medicatie en functionele gezondheidstoestand **(hoofdstuk vier)**. In vijf praktijken werd gedurende een jaar het model van gedeelde zorg toegepast, in vier praktijken werd gebruikelijke zorg geleverd. Het model bestond uit een training voor medewerkers, gestructureerde zorg door een praktijk ondersteuner en de mogelijkheid om een nefroloog te raadplegen in een beschermde digitale omgeving (telenefrologie). 164 patiënten met diabetes en/of hoge bloeddruk en een verminderde nierfunctie (eGFR $<$ 60 ml/min/1.73 m^2) konden geanalyseerd worden. Na een jaar studie was de bloeddruk in de interventie groep (134.7/73.8 mmHg) lager dan in de controle groep (142.9/80.9 mmHg). De bloeddruk daalde met 8.1/1.1 mmHg in de interventie groep en steeg met 0.2/0.5 mmHg in de controle groep. De verbetering in bloeddrukwaarden in de interventie groep liep parallel aan een verhoogd gebruik van bloeddruk verlagende middelen (RAAS remmers). De bloedwaarden van parathormoon was 6.1 pmol/l in de interventie groep en 8.2 pmol/l in de controle groep. Dit liep parallel aan een frequenter gebruik van vitamine D. Cholesterol en LDL-cholesterol waarden daalden in de interventie groep tijdens het jaar. Dit liep samen op met een verhoogd gebruik van cholesterol verlagende middelen.

Aangezien bloeddruk de meest belangrijke beïnvloedbare risicofactor is voor een ongunstig beloop van CNS, concludeerden wij dat een model van gedeelde zorg van waarde kan zijn voor patiënten met CNS in de eerste lijn.

5. Praktische toepassing en haalbaarheid van web-based consultatie tussen huisarts en nefroloog

Tijdens de SHARING studie ontwikkelden we een web-based consultatie systeem: telenefrologie. Met dit systeem kunnen relevante gegevens uit het huisarts informatie systeem van de huisarts geëxporteerd worden naar een digitale omgeving waarin de nefroloog een advies kan geven. In **hoofdstuk vijf** beschrijven we de bevindingen bij 122 telenefrologie-consultaties door 28 huisartspraktijken en vijf nefrologie afdelingen. We waren geïnteresseerd in de mogelijkheid tot het verminderen van verwijzingen. Dit hebben we gemeten als het verschil tussen het aantal verwijzingen dat de huisarts had willen doen (als er geen telenefrologie was geweest) en het aantal verwijzingen wat de nefroloog noodzakelijk achtte. We konden 122 consultaties analyseren. Zonder telenefrologie zouden 43 patiënten (35.3%) door hun huisarts verwezen zijn, terwijl de nefroloog slechts bij 17 patiënten (13.9%) verwijzing nodig vond. De huisarts had 79 patiënten in eigen beheer willen behandelen. Bij tien van deze patiënten vond de nefroloog het verstandiger de patiënt wel te verwijzen. Het systeem was praktisch toepasbaar: het werd vooral tijdens kantoortijden gebruikt en de gemiddelde consult-duur was slechts negen minuten.

We concludeerden dat een web-based consultatie systeem het aantal verwijzingen zou kunnen verminderen. Op die manier zou telenefrologie kunnen bijdragen aan een efficiënt gebruik van gezondheidszorgvoorzieningen doordat patiënten in de eerste lijn behandeld kunnen worden met kennis uit de tweede lijn.

6. Wat zou de samenwerking tussen huisarts en apotheker kunnen bijdragen aan medicatie veiligheid bij patiënten met CNS en diabetes of hoge bloeddruk?

Er zijn verschillende redenen waarom de medicatie veiligheid bij patiënten met CNS in het geding kan zijn: ten gevolge van verminderde nierfunctie worden sommige geneesmiddelen niet goed uit het lichaam verwijderd waardoor de geneesmiddelspiegel in het lichaam te hoog kan worden, er zijn geneesmiddelen die de nier rechtstreeks beschadigen en er zijn middelen die de bloeddoorstroming door de nier verminderen en daarmee schade aan de nier toebrengen. Als huisartsen en apothekers samen werken zou dat kunnen bijdragen aan het herkennen en verminderen van medicatie fouten. In **hoofdstuk zes** beschrijven we een samenwerkingsmodel tussen huisarts en apotheek, waarbij de apotheek kon beschikken over nierfunctie waarden van oudere patiënten die geneesmiddelen gebruikten voor diabetes of hart -en vaatziekten. In één op de negen recepten adviseerde de apotheker een wijziging aan te brengen. De huisarts woog deze adviezen in het licht van de klinische context van de patiënt. Vervolgens besloot de huisarts de helft van de adviezen over te nemen. Dit leidde er toe dat de huisartsen zich voornamen om in 5% van de onderzochte voorschriften een wijziging aan te brengen. We concludeerden dat samenwerking tussen huisarts en apotheker kan bijdragen aan patiënt veiligheid, omdat beide disciplines vanuit verschillende invalshoeken expertise in brengen.

7. Onderzoek naar bloeddrukmeting

De hoogte van de bloeddruk houdt verband met de prognose op het gebied van hart -en vaatziekten en van nierfalen bij CNS patiënten. Om een goede behandeling te kunnen inzetten, dient de bloeddruk zorgvuldig gemeten te worden. In **hoofdstuk zeven** onderzochten wij de nauwkeurigheid van een 30-minuten bloeddruk meting. Deze meet methode, waarbij de patiënt gedurende 30 minuten alleen in een kamer zit, waarbij een aantal malen de bloeddruk wordt gemeten, bleek tot lagere meetwaarden te leiden dan een keurig volgens de regels uitgevoerde spreekkamer bloeddruk meting. Dit komt vermoedelijk omdat het zogenaamde ‘witte jassen effect’ een kleinere rol speelde bij de 30-minuten bloeddruk meting dan bij de spreekkamer bloeddruk meting. Bij herhaling van de meting bleken de resultaten van de 30 minuten meting beter te reproduceren te zijn dan die van een gewone spreekkamer bloeddrukmeting.

Naar aanleiding van onze onderzoeksbevindingen hebben we een aantal aanbevelingen gedaan voor de dagelijkse praktijk en voor toekomstig onderzoek.

Aanbevelingen voor de dagelijkse praktijk:

1. Feedback aan huisartspraktijken op basis van laboratorium uitslagen zou een goede manier kunnen zijn om praktijken te helpen om de patiënten met CNS te herkennen.
2. Praktijkondersteuners kunnen bijdragen aan de kwaliteit van zorg door de reguliere controles te verzorgen. Dit is goed in te bedden in de bestaande diabetes en hypertensie zorg.
3. Controle van metabole problemen zou kunnen verbeteren door meer scholing te verzorgen over dit onderwerp. Feedback op basis van laboratorium uitslagen kan duidelijk maken welke patiënten in aanmerking komen voor controle van calcium, fosfaat en PTH. Telenefrologie zou kunnen bijdragen aan verspreiding van kennis over metabole problemen. Het is nog niet bekend of behandeling van een verhoogd PTH in de eerste lijn daadwerkelijk bijdraagt aan een betere prognose. Deze fundamentele vraag zal eerst beantwoord moeten worden.
4. De behandeling van de bloeddruk bij patiënten met CNS verdient meer aandacht in de eerste lijn. De behandeldoelen werden vaak niet gehaald. Aan de andere kant is het belangrijk dat de bloeddruk niet over-behandeld wordt, zeker niet bij kwetsbare ouderen.
5. Van de patiënten waarbij de richtlijn verwijzing adviseert, werd slecht een klein percentage daadwerkelijk verwezen. Dit kan samenhangen met een lage herkenning van patiënten, met een slechte gezondheidstoestand van de patiënt waardoor de huisarts het nut van verwijzing laag inschat of met het feit dat de huisarts de richtlijn niet onderschrijft. Immers: een verminderde nierfunctie komt veel voor bij oudere patiënten en het is nog niet goed uitgekristalliseerd in hoeverre een intensieve behandeling bijdraagt aan een betere prognose bij oudere patiënten. Meer kennis daarover zou behandelbeslissingen bij deze groep kunnen ondersteunen.
6. De apotheker dient te kunnen beschikken over actuele nierfunctie waarden. Daarvoor is niet alleen nodig dat de nierfunctie waarden inzichtelijk zijn voor de apotheker, maar ook dat risico patiënten op zijn minst jaarlijks worden gecontroleerd. Idealiter worden in de toekomst kenmerken van de patiënt mee gewogen bij de automatische medicatie bewaking.

Aanbevelingen voor onderzoek:

- Bestudeer patiënt voorkeuren daar waar het gaat om behandeling in eerste of tweede lijn. Onderzoek mogelijkheden om self-management uit te breiden.
- Verricht nader onderzoek bij huisartsen naar hun mening over de behandel en verwijs adviezen uit de richtlijn en hun overwegingen wanneer de richtlijn niet gevolgd wordt.
- Probeer vast te stellen welke oudere patiënten met CNS in de eerste lijn gebaat zijn bij behandeling.
- Bestudeer het effect van PTH verlaging op het verminderen van hart- en vaatziekten bij patiënten in de eerste lijn.
- Onderzoek mogelijkheden om patiënten uit de tweede lijn terug te verwijzen naar de eerste lijn met ondersteuning van telenefrologie.

CONCLUSIE

Op het gebied van CNS hebben veel spelers een rol: patiënt, praktijkondersteuner, huisarts, apotheker en nefroloog hebben ieder een duidelijke omschrijving van taken en verantwoordelijkheden nodig. Niet alleen richtlijnen, maar ook implementatie hulpmiddelen die praktische en mentale barrières helpen overwinnen, zijn nodig om ieder zijn rol optimaal te doen vervullen. In de samenwerking tussen de verschillende spelers is nog een wereld te winnen als gedeelde zorg het uitgangspunt is en als onderlinge communicatie wordt ondersteund met ICT hulpmiddelen. Het resultaat zou moeten zijn dat optimale zorg wordt gerealiseerd in samenwerking met de patiënt in zijn eigen omgeving.

TEAMWORK!

'Is shared care the answer?' is de vraag in de subtitel van dit proefschrift. Als het gaat over de totstandkoming van dit proefschrift had er moeten staan: shared care ìs the answer!! Want wat een teamwork was dit promotie traject. Het aantal mensen wat samen met mij hieraan heeft gewerkt overschrijdt ruimschoots de bemanning van een acht, het zou een hele vloot worden. Ik bedank iedereen die een bijdrage heeft geleverd!

Coaches

Chris van Weel, beste Chris. Mijn dank betreft jouw overstijgende blik op het onderzoek, de snelle en behulpzame reacties op steeds weer nieuwe versies van artikelen, je rijke taalgebruik. Heel dankbaar ben ik je ook voor de bespiegelende gesprekken, jouw stimulans om het academische spoor verder te volgen en over de grens te kijken.

Jack Wetzels, beste Jack. Ik heb geweldig genoten en geprofiteerd van jouw gedrevenheid. Er zijn veel mensen in het Radboud die hard werken, maar jij breekt wel alle records. Zo langzamerhand ken ik je werkpatroon: zondagochtend kwamen de meest gedetailleerde reacties. Dank voor al je hulp en geduld en je betrokkenheid bij de eerste lijn.

Wim de Grauw, beste Wim. Toen ik voorzichtig overwoog om het roer tijdelijk om te gooien van opleiding naar onderzoek, heb jij me over de streep getrokken met je enthousiasme. Je straalde uit dat onderzoek doen heel leuk is. En dat is het ook als je met iemand zoals jij kunt werken! Dank voor alle gezellige uren dat we discussieerden over het leven in het algemeen (wat is er privé veel gebeurd in die paar jaar) en het onderzoek. Naast passie voor onderzoek heb je grote passie voor je patiënten, die met chronische nierschade in het bijzonder. Tijdens de Sharing studie bleek er in jouw praktijk in Berghem een overmaat aan patiënten met chronische nierschade te zijn. We hebben dit het Wim de Grauw-effect gedoopt.

Gerald Vervoort, beste Gerald. Jij liep helemaal warm voor de Telenefrologie. Binnen de kortste keren hadden we een beeld waar het op zou moeten gaan lijken en zo is het ook geworden, mede dankzij jouw input. Met verve gaf jij de scholing aan de praktijken die participeerden in de studies. Dank daarvoor en voor het meedenken over methodologie en uitvoering van de studies.

Ben Bottema, beste Ben, ook jou wil ik bedanken voor de stimulans om onderzoek te gaan doen. De timing kwam zeer ongelukkig uit, zo net voor de start van een nieuwe

groep huisartsen in opleiding. Ik vind het bijzonder dat ik nu in een deel van jouw voetsporen treed.

Jozé Braspenning, beste Jozé, dank voor jouw koers bepalende uitspraken.

Project bemanning

Dit proefschrift bestaat uit vier projecten. Elk project had zijn eigen bemanning. Een bemanningslid wat bijna overal opdook was Lea Peters. Allerbeste Lea, jij bent de smeerolie richting praktijken, rond data verzameling en registratie. En alsof dat nog niet genoeg is, jouw monterheid om elk probleem te tackelen gaf mij steeds weer een goed humeur. Voor het Sharing project over gedeelde zorg tussen huisarts, praktijkondersteuner en nefroloog dank ik alle patiënten die bereid waren de metingen te ondergaan. De inzet van de praktijkondersteuners uit de praktijken van het Nijmeegs Monitoring Project was buitensporig, dank daarvoor! José van Boxtel wil ik hier met name even noemen: altijd stond je klaar om ons weer een stapje verder te helpen. Het praktisch meedenken van Wouter Koop van het klinisch chemisch laboratorium van het CWZ in Nijmegen (tot aan het zelf ophalen van bloed in Doesburg toe!) was van onschatbare waarde. Tijdens de Sharing studie ontwikkelden we Telenefrologie. Janneke Remmelts en Pieter Jeekel hebben daar een grote bijdrage aan geleverd. Vincent van Gelder hield zich als student bezig met de evaluatie van de eerste Telenefrologie consulten. Wat waren we blij dat hij de uitnodiging aannam om er een heel promotie traject van te maken. Vincent, je gaf me geweldig veel energie met je enthousiasme en helder verstand! Alle succes met je promotie en je opleiding! Jij gaat nu verder met de resultaten uit de grote Contact studie, die onderzoekt wat het effect is van Telenefrologie op verwijzingen en kwaliteit van zorg. Maar liefst 47 praktijken deden daar aan mee en de nefrologen van 5 ziekenhuizen: UMC St Radboud, Rijnstate, Gelderse Vallei, Bernhoven en CWZ. Veel dank aan alle huisartsen, praktijkondersteuners en nefrologen. Meedoen aan zorg innovatie kan heel leuk zijn, maar niemand zit te wachten op gedoe zoals het invullen van lijstjes, zelfs niet als het een trendy app is. Fijn dat jullie dat wilden doen! Dankzij de medisch studenten Niki Pernot en Inge de Grauw hebben we al veel data uit de Contact studie kunnen verwerken. Dat al die data boven tafel kwamen en geanalyseerd werden, hebben we te danken aan mensen die daar goed in zijn. José Donkers, Marion Biermans, Jan Mulder en Reinier Akkermans, dank voor alle hulp!

Dan was er het SKIP project, over de samenwerking tussen huisarts en apotheker met als doel de medicatieveiligheid te vergroten. Arjen Geerts, Fred de Koning, Peter de Smet en alle apothekers van de Kring-apotheken in Arnhem noord en de huisartsen uit de FTO groep waren van onschatbare waarde. Ook de klinisch chemici

van het Rijnstate ziekenhuis en het SHO waren ons behulpzaam. Tim van der Sterren leidde als medisch student alles in goede banen. Ik dank iedereen van harte voor hun medewerking.

Voor de 30 minuten bloeddrukmetingen vormden Carel Bakx, Mark van der Wel en Theo Thien de stuurlui. Het was een genoegen om aan te schuiven bij de dinsdag-ochtend sessies. In die kamer vol boeken en artikelen ontstonden de meest sprankelende ideeën. Na het overlijden van Carel zal het nooit meer hetzelfde zijn. Steve Boudewijns en Gijs Schoenmakers deden de metingen in Berghem en Schaijk, dank aan hen en alle patiënten!

Diverse bemanning

De dames van het secretariaat van de opleidingen en van het onderzoek verdienen zeer veel lof! Wat een bereidheid om altijd weer te helpen, menig bedrijf kan daar jaloers op zijn!

De gezelligheid van mijn kamergenoten Els Pelgrim, Thea van Roermund, Patrick Dielissen en van de gang op de derde verdieping (allemaal mensen-met-een-mening) maakte dat ik altijd met plezier naar mijn werk ging en me kon verheugen op de leuke discussies.

Dank aan de medewerkers van Thermion voor alle flexibiliteit!

Dan Lasserson, hoi Dan, thank you for being part of the mansuscript committee. The Oxford-Nijmegen renal consortium has a promising potential! If you teach me how to publish in the BMJ, I will help you with the BJGP.

Malcolm Falkus, dear Malcolm. I appreciate our special friendship. We met on many different places on different occasions, happy and sad. Thank you so much for critically reading the manuscripts.

Thuishaven

Dit proefschrift was er nooit gekomen zonder de bijstand van onze gouden hulpen: Bets, Ans, Suzan, Elsje en Lula, dank jullie wel voor alles wat jullie voor ons gezin betekenen!

Ik heb genoten van het promotie traject. Maar onze kinderen zouden zeggen YOLO, Lekker Belangrijk zo'n boekje. Er zijn veel leuker dingen te doen! Liefst met mijn fijne familie en vrienden. Het zou te ver gaan om jullie te bedanken voor jullie hulp bij het

proefschrift. Het is meer ondanks jullie dat het gelukt is. Diep in mijn hart was ik namelijk liever veel vaker ingegaan op jullie verleidingen om vakantie te vieren, te hockeyen, rennen, wandelen, zwemmen, skiën, film te kijken, koken, eten, muziek te maken of te luisteren.

Mijn broer, lieve Enno, wat leuk dat je nu weer ceremonie meester zal zijn, net als bij ons trouwen! Je bent een meester in organiseren, of het nou voor de zeilvereniging is of voor een project in Thailand, het komt allemaal strak voor elkaar.

Bart de Koning, lieve Bart. Super dat je mijn paranimf kunt zijn. We hebben samen de praktijk in Santpoort-Noord gerund. Dat was een gouden tijd. Ik had mij geen fijnere collega kunnen wensen. Dat we ook nog in dezelfde levensfase zaten en met onze gezinnen op Vlieland of Terschelling vakantie hielden was nog eens mooi meegenomen.

Angela Spit, lieve Angela, al vanaf onze studie in Groningen hebben we veel gemeenschappelijk gedaan. Fijn dat je me straks zal helpen door te zeggen dat controle albuminurie over een jaar zeker geindiceerd is! Ik bewonder hoe je alles voor elkaar krijgt en ik waardeer jouw attente belangstelling geweldig. Allebei zouden we graag meer tijd hebben voor de leuke dingen van het leven. Als een kampeerweekendje of een running-date lukt, zijn we helemaal blij.

Dankbaar ben ik voor de warmte en ruimte waarin ik ben opgegroeid. Graag noem ik op deze plek mijn ouders Hanna en Hidde. Zij zijn er niet meer, maar ik voel ze nog dagelijks om mij heen. Hidde, met zijn credo 'deze dag komt tot ons als een geschenk'. Voor mij staat dat voor levenslust. Wat had hij de promotie graag mee willen maken! Tekenend voor mijn lieve moeder Hanna was: 'zoals een gewas het licht zoekt, zoekt de mens het geluk'. Haar wijsheid en mildheid inspireren mij. Ook haar Dolf, met zijn grote belangstelling, is niet meer bij ons, maar Marja vormt een mooi schakeltje naar die tijd. In de serie ouderfiguren horen zeker ook Pieter en Betty Faber. Er is niemand die mij zo lang en goed kent als jullie. Heel graag laat ik mij voeden op vele fronten in jullie gastvrije huis aan de IJssel. En dan nog meer ouders! Lieve Gerd, samen met jouw fantastische Janny, die helaas sinds vorig jaar niet meer leeft, ben je altijd vol belangstelling, en altijd vol raad en daad, ook ongevraagd! Het was heerlijk om bij jou te kunnen schrijven (ook al bij de IJssel..). Het vooruitzicht dat je straks in de corona zal zitten, maakt voor mij de dag bij voorbaat geslaagd! Eén van de beste dingen die jullie gedaan hebben is hele fijne kinderen voort brengen: Harm, Marieke en Jan-Jaap. Laat ik nou met die laatste getrouwd zijn. Lieve Jan-Jaap, jij maakt het allemaal mogelijk, zorgt dat het gezellig blijft en maakt alles meer dan de moeite waard. Hanna Yu, Xiaodong en Yuan, grote lieverds, het is een feest om jullie te zien opgroeien! Graag gaan we met jullie de toekomst tegemoet!

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CURRICULUM VITAE

Nynke Scherpbier-de Haan was born in Oegstgeest in 1964. Her childhood she spent in France and Soest. She went to grammar school (Johan van Oldenbarnevelt gymnasium) in Amersfoort, and started her study medicine in Groningen in 1982. Her internships were in Deventer, Bandung and Malawi. After her graduation in 1989 she worked as a resident on various departments of 'Het Spittaal' in Zutphen and as a resident in internal medicine in Apeldoorn. In 1992 she started vocational training in general practice at the University of Amsterdam, with traineeships in 't Zand with Jan Kos and in Haarlem with Bob Stapel. Afterwards she worked in Uitgeest and Santpoort-Noord. In 1997 she settled in Santpoort-Noord as a general practitioner. Postgraduate education was one of her activities in that time. She initiated and coordinated the building of a health centre, but did not have the chance to work there due to a move to Arnhem in 2004. There she combined her work in general practice with being a teacher for GP trainees at the Radboud University in Nijmegen. She followed a 2 year training on organisation and management in primary care. In the end of 2007 she started a research project on the management of Chronic Kidney Disease and was active in the development of Telenephrology. Since 2011 she works one day a week in Thermion, an academic health centre in Lent. In 2013 she was appointed as Deputy Head of the Primary care vocational training department, Radboud University Medical Centre, Nijmegen. She is happily married with Jan-Jaap Scherpbier. They have three wonderful children: Hanna Yu, Xiaodong and Yuan.