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# Multifactorial intervention with nurse practitioners does not change cardiovascular outcomes in patients with chronic kidney disease

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**Strict implementation of guidelines directed at multiple targets reduces vascular risk in diabetic patients. Whether this also applies to patients with chronic kidney disease (CKD) is uncertain. To evaluate this, the MASTERPLAN Study randomized 788 patients with CKD (estimated GFR 20–70 ml/min) to receive additional intensive nurse practitioner support (the intervention group) or nephrologist care (the control group). The primary end point was a composite of myocardial infarction, stroke, or cardiovascular death. During a mean follow-up of 4.62 years, modest but significant decreases were found for blood pressure, LDL cholesterol, anemia, proteinuria along with the increased use of active vitamin D or analogs, aspirin and statins in the intervention group compared to the controls. No differences were found in the rate of smoking cessation, weight reduction, sodium excretion, physical activity, or glycemic control. Intensive control did not reduce the rate of the composite end point (21.3/1000 person-years in the intervention group compared to 23.8/1000 person-years in the controls (hazard ratio 0.90)). No differences were found in the secondary outcomes of vascular interventions, all-cause mortality or end-stage renal disease. Thus, the addition of intensive support by nurse practitioner care in patients with CKD improved some risk factor levels, but did not significantly reduce the rate of the primary or secondary end points.**

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**Received 14 October 2011; revised 13 January 2012; accepted 7 February 2012; published online 27 June 2012**

*Kidney International* (2012) **82,** 710–717; doi:10.1038/ki.2012.137; published online 27 June 2012

KEYWORDS: blood pressure; cardiovascular event; chronic kidney disease; epidemiology and outcome

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

The aim of our study was to assess whether the addition of nurse practitioner care to standard care by a nephrologist in patients with moderate-to-severe CKD, aimed at strict implementation of current guidelines with emphasis on CVD medication and lifestyle changes, improves cardiovascular outcome.[16]

## RESULTS

About 60% of patients deemed eligible by their physician and asked to participate in the study actually participated and were included. Non-participation was mainly because of reluctance to change drug therapy and inability to attend the required visits.

Between April 2004 and December 2005 we randomized 793 patients (Figure 1). Three patients did not meet inclusion criteria and two declined participation directly after randomization. Thus, 788 patients were included in the study: 393 in the control group and 395 in the intervention group. Characteristics were well balanced between groups apart from a history of CVD, which was more common, and current smoking, which was less prevalent in the intervention group (Table 1).

The clinical characteristics of the 110 transplant recipients were: 59% men, 92% Caucasian, age 51 (12) years, estimated glomerular filtration rate 40 (13) ml/min per 1.73 $m^2$. Mean duration after transplantation was 7.5 (5.4) years. In all, 73% used a calcineurin inhibitor, 68% used an antimetabolite (i.e., mycophenolate or azathioprine), and 74% had steroids.

Mean follow-up duration for the entire cohort was 4.62 years (median: 4.83; interquartile range 4.44 to 5.36). Follow-up was concluded in May 2010.

### Effect on targeting risk factors

During the follow-up, mean office blood pressure (BP) was significantly lower in the intervention group (132/77 mm Hg) than in the control group (135/79 mm Hg). Similar differences were found for oscillometric BP measurements (Table 2). Significant differences were found for low-density lipoprotein (LDL) cholesterol (−0.11 mmol/l (−4 mg/dl)), triglycerides (−0.15 mmol/l (−13 mg/dl)), hemoglobin (+0.01 mmol/l) (+0.02 g/dl), anemia (−2%), proteinuria (−0.12 g per 24 h) and use of active vitamin D (or analogs) (+4.6%), aspirin (+10%), and statins (+4.7%). The number of antihypertensive drugs was higher and increased more in the intervention arm (3.16 vs. 3.04; $P = 0.04$). Use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers showed a trend of increased use in the intervention arm (+2.6%; $P = 0.07$). No differences were found for smoking, body weight, sodium excretion, physical activity, or glycemic control (Table 2). The magnitude of the differences was small, despite its statistical significance (Figure 2, Table 2 and Supplementary Figure S1 online).

In the control group, similar beneficial trends were seen, leading to smaller differences between treatment groups. This is illustrated for oscillometric BP measurements, lipid lowering drugs, and for platelet aggregation inhibitors (Figure 2). Identical patterns of changes in lifestyle factors were observed in both treatment arms for body mass index and smoking (Supplementary Figure S2 online).

In patients who at baseline had proteinuria >0.5 g per 24 h, mean proteinuria during follow-up in the intervention group was 1.7 g per 24 h and in the control group 1.9 g per 24 h ($P = 0.08$).

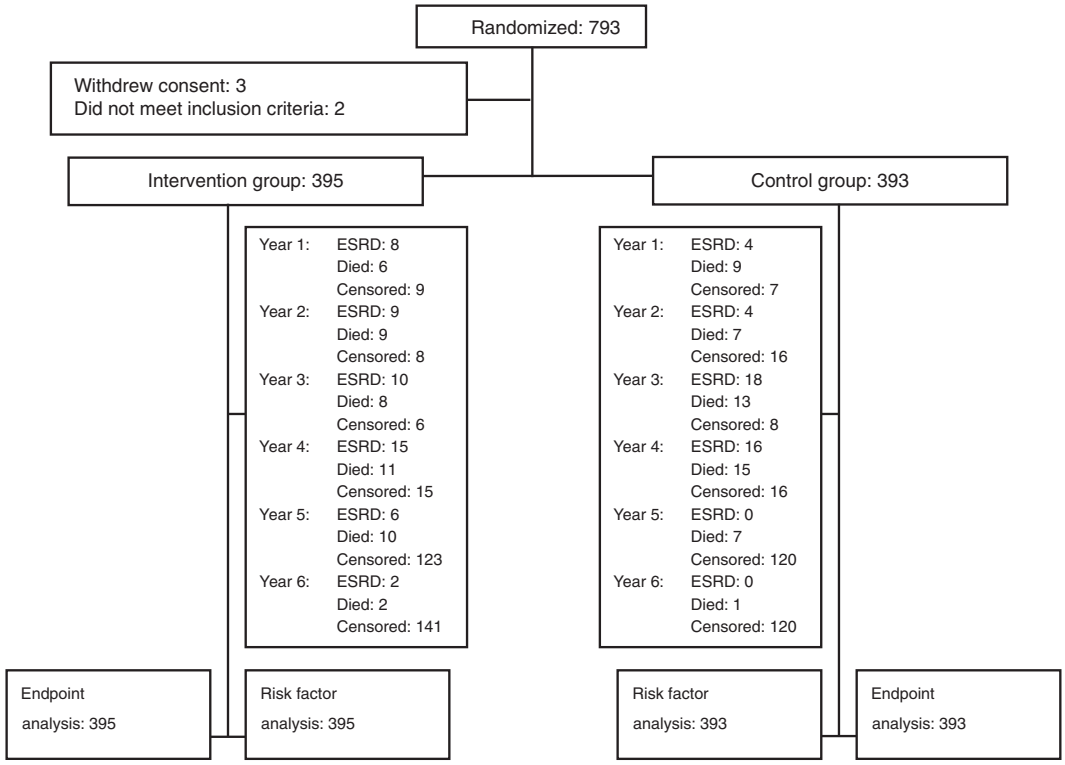


**Figure 1 | Flow chart of participants.** Censored means lost to follow-up (not due to ESRD or death), because of moving to another hospital, end of study, or failure to contact the participant. ESRD, end-stage renal disease (either dialysis or transplantation).

**Table 1 | Characteristics of participants at baseline by assigned treatment**

| Parameter | Control group (*n*=393) | Intervention group (*n*=395) | *P*-value |
|---|---|---|---|
| Age (years) | 59.3 (12.8) | 58.9 (13.1) | 0.60 |
| Gender (male) (%) | 68 | 67 | 0.82 |
| Race (Caucasian) | 93 | 91 | 0.65 |
| *Nephrological diagnosis (%)* | | | 0.06 |
| Diabetic nephropathy | 9 | 11 | |
| Renovascular | 28 | 26 | |
| Glomerulonephritis/interstitial nephritis | 34 | 28 | |
| Congenital disease | 13 | 11 | |
| Unknown | 16 | 24 | |
| Kidney transplantation (%) | 14 | 14 | 1.0 |
| Prior cardiovascular disease by questionnaire (%) | 25 | 33 | 0.02 |
| Creatinine (μmol/l) | 181 (67) | 182 (64) | 0.76 |
| eGFR (ml/min per 1.73 $m^2$)[a] | 37.7 (14.0) | 38.4 (15.2) | 0.66 |
| Office BP (mm Hg) | 139 (22)/81 (11) | 138 (20)/80 (11) | 0.90/0.43 |
| Oscillometric BP (mm Hg) | 136 (21)/79 (11) | 135 (20)/78 (11) | 0.46/0.36 |
| Proteinuria (g per 24 h)[b] | 0.3 (0.1–0.8) | 0.2 (0.1–0.8) | 0.27 |
| LDL cholesterol (mmol/l) | 2.74 (0.90) | 2.78 (0.95) | 0.70 |
| Hemoglobin (mmol/l) | 8.2 (1.0) | 8.2 (1.0) | 0.88 |
| History of DM (%)[c] | 23 | 25 | 0.37 |
| Phosphate (mmol/l) | 1.10 (0.25) | 1.11 (0.25) | 0.98 |
| PTH (pmol/l)[b] | 9 (5–14) | 9 (5–15) | 0.74 |
| Sodium excretion (mmol per 24 h)[b] | 150 (113–189) | 148 (116–195) | 0.89 |
| BMI (kg/$m^2$) | 27.2 (4.9) | 27.0 (4.6) | 0.53 |
| Physical activity (%)[d] | 60 | 57 | 0.23 |
| Smoking (%) | 24 | 19 | 0.04 |
| Pack years (years) | 6.5 (1.8–16.3) | 6.3 (0–11.8) | 0.13 |

Abbreviations: BP, blood pressure; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; PTH, parathyroid hormone.
[a]Based on the Modification of Diet in Renal Disease formula.
[b]Median (25th–75th percentile).
[c]History of diabetes mellitus defined as using blood glucose lowering medication or fasting glucose >7.0 mmol/l.
[d]Adherence to Dutch physical activity guideline.
Values are proportions, means with corresponding s.d., or median with interquartile ranges, when appropriate.
Conversion factor to mg/dl: creatinine 0.0113, LDL cholesterol 38.6, glucose 18, phosphorus 3.1; conversion factor to g/dl: hemoglobin 1.62; conversion factor to pg/ml: PTH 9.1.

### Effect on end points

A total of 80 participants had a major nonfatal or fatal CVD event during follow-up (Table 3). Intensive control did not reduce the rate of the composite end point (21.3/1000 person-years in the intervention group vs. 23.8/1000 person-years in the control group; hazard ratio (HR) 0.90 (95% confidence interval (CI) 0.58, 1.39, $P=0.63$)). The data safety monitoring board also reported their results for the primary end point adjusted for the sequential analysis (HR 0.84 (95% CI 0.45, 1.35), $P=0.48$).

As history of CVD and diabetes were not distributed equally in the two groups because of chance, an additional analysis was performed. With adjustment for history of CVD and baseline smoking the HR was 0.80 (95% CI 0.55–1.25).

No statistically significant differences were found in secondary event outcomes, including end-stage renal disease (dialysis and/or transplantation) (28.6 vs. 34.4/1000 person-years; HR 0.83 (95% CI 0.57, 1.20), $P=0.32$). Subgroup analyses for baseline parameters such as age, gender, BP, baseline estimated GFR calculated by the Modification of Diet in Renal Disease formula, and previous CVD history showed no heterogeneity for the composite end point (all *P*-values for the interaction terms >0.20). For kidney transplantation, the *P*-value of the multiplicative interaction term in Cox model for the composite end point was 0.41 and for all-cause mortality 0.16, for a history of diabetes the *P*-value of the multiplicative interaction term in Cox model for the composite end point was 0.88.

### Number of visits to the outpatient clinic department

The mean number of annual outpatient clinic visits (physician and/or nurse practitioner) during the first 2 years was significantly higher in the intervention group than in the control group (7.2 vs. 4.7; $P<0.001$). The mean number of physician visits in the intervention group was significantly lower than in the control group (2.8 vs. 3.7; $P<0.001$).

### Quality of life by EQ-5D

In both intervention and control group, a gradual rise in quality of life assessed by EQ-5D could be found. Baseline score was 0.80 in both groups and increased to 0.83. However, there was no difference for quality of life between intervention and control ($P=0.79$).

## DISCUSSION

This study shows that nurse practitioner–assisted care targeting multiple risk factors in CKD results in better BP control and lipid management, less proteinuria and the increased use of antihypertensives, statins, aspirin, and active vitamin D. Lifestyle interventions are ineffective. Intensive control has no effect on clinical outcome.

Several trials reported an improvement in CVD risk factor management by nurse practitioner support in patients with diabetes or otherwise high CVD risk, with particular effect on medication-dependent risk factors, such as BP and cholesterol.[13,17–21] Our study confirms that notion.

Some other studies need to be discussed in some detail. The first is the Steno-2 study, which served as an example for our study. It reported not only better risk factor management, but also a substantial improvement in clinical outcome, which contrasts with our results. This may be explained, at least partially, by some differences between the studies. All patients in the Steno-2 study had type 2 diabetes, and thus another *a priori* cardiovascular risk. Moreover, these patients had higher BP and cholesterol at baseline. As a consequence, larger improvements in BP (systolic 11 mm Hg, diastolic 4 mm Hg), and LDL cholesterol (0.8 mmol/l (31 mg/dl)) could be obtained. Further, the Steno investigators reported large differences in the quality of glucose management and in the use of aspirin between treatment arms. There is also an important design difference between the studies. In Steno-2,

**Table 2 | Effects of strict implementation of the guidelines on various risk factors during follow-up using the intention-to-treat principle with complete follow-up**

| | Mean levels at baseline | | Mean level during follow-up[a] | | | | |
|---|---|---|---|---|---|---|---|
| Risk factor | Control | Intervention | Control | Intervention | Mean difference[a] | s.e. | *P*-value for difference |
| MDRD (ml/min per 1.73 $m^2$) | 38.1 | 39.4 | 35.8 | 36.6 | 0.82 | 0.49 | 0.10 |
| Systolic office BP (mm Hg) | 139 | 138 | 135 | 132 | −3 | 0.77 | <0.001 |
| Diastolic office BP (mm Hg) | 81 | 80 | 79 | 77 | −2 | 0.45 | <0.001 |
| Systolic oscillometric BP (mm Hg) | 136 | 135 | 132 | 129 | −3 | 0.61 | 0.002 |
| Diastolic oscillometric BP (mm Hg) | 79 | 78 | 77 | 75 | −2 | 0.49 | <0.001 |
| LDL cholesterol (mmol/l) | 2.74 | 2.78 | 2.50 | 2.39 | −0.11 | 0.04 | 0.008 |
| HDL cholesterol (mmol/l) | 1.31 | 1.31 | 1.26 | 1.29 | 0.03 | 0.019 | 0.15 |
| Triglycerides (mmol/l) | 1.89 | 1.80 | 1.89 | 1.74 | −0.15 | 0.06 | 0.009 |
| Proteinuria (g per 24/h) | 0.81 | 0.76 | 0.77 | 0.65 | −0.12 | 0.06 | 0.04 |
| Hemoglobin (mmol/l) | 8.2 | 8.2 | 8.0 | 8.1 | 0.10 | 0.04 | 0.03 |
| Phosphate (mmol/l) | 1.10 | 1.11 | 1.15 | 1.13 | −0.01 | 0.016 | 0.43 |
| PTH (pmol/l) | 11.7 | 10.8 | 13.7 | 13.3 | −0.38 | 0.67 | 0.57 |
| HbA1c (%) | 6.1 | 6.1 | 6.3 | 6.3 | −0.003 | 0.05 | 0.96 |
| HbA1c (%) in diabetics (*n*=193) | 6.9 | 6.9 | 7.1 | 7.0 | 0.10 | 0.09 | 0.25 |
| BMI (kg/$m^2$) | 27.2 | 27.0 | 27.0 | 27.1 | 0.02 | 0.11 | 0.88 |
| Sodium excretion (mmol per day) | 155 | 156 | 155 | 156 | 1.15 | 3.12 | 0.72 |
| Physical activity (%)[b] | 60 | 57 | 58 | 62 | 3.8 | 2.6 | 0.15 |
| Smoking (%) | 24 | 19 | 14 | 14 | 0.0 | 0.007 | 0.73 |
| No. antihypertensive drugs | 3.0 | 2.9 | 3.04 | 3.16 | 0.12 | 0.06 | 0.04 |
| Use of ACEi and/or ARB (%) | 78 | 81 | 85 | 87 | 2.6 | 1.4 | 0.07 |
| Statin use (%) | 63 | 67 | 76 | 80 | 4.7 | 1.55 | 0.002 |
| Antiplatelet drugs (%)[c] | 39 | 45 | 57 | 67 | 9.6 | 2.4 | <0.001 |
| Glucose lowering drugs (%) | 19 | 21 | 21 | 20 | −0.03 | 1.17 | 0.73 |
| Vitamin D (%) | 24 | 22 | 41 | 46 | 4.6 | 2.0 | 0.02 |
| Phosphate binders (%) | 13 | 9 | 18 | 16 | 1.3 | 1.5 | 0.14 |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; GEE, generalized estimating equation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease formula; PTH, parathyroid hormone.
[a]Mean difference over time in risk factor levels between treatment arms obtained through GEE analyses using the on trial measurements with adjustments for baseline measurements. Complete follow-up means that all individuals have been followed with respect to the risk factor measurements also when they suffered a non-fatal event or received kidney transplant or a renal replacement therapy.
[b]Adherence to Dutch physical activity guideline.
[c]In those not using oral anticoagulant drugs treatment at baseline.
Conversion factor to mg/dl: creatinine 0.0113, LDL cholesterol 38.6, glucose 18, phosphorus 3.1; conversion factor to g/dl: hemoglobin 1.62; conversion factor to pg/ml: PTH 9.1.

control patients remained in the care of a general practitioner, whereas study patients were treated by a team led by a nurse practitioner in a highly specialized diabetes clinic.

Two studies in CKD patients are available. A recent randomized trial with 2 years follow-up (CanPREVENT) in 474 CKD patients compared care coordinated by nurses under nephrologist supervision with that of general practitioners.[22] They found no effect on risk factor control or on clinical end points. However, some important differences exist between that and our study. For instance, patients in CanPREVENT had better preserved kidney function, less proteinuria, at baseline already good BP control (130/74 mm Hg) and low LDL cholesterol. Further, follow-up was limited to 2 years.

In an older study, the effects of an intensive treatment regimen in 200 patients with CKD stage IV and V, of whom 65% were on dialysis at the start of the study, were reported.[23] BP was −6.7/−3.8 mm Hg and LDL cholesterol 0.4 mmol/l (15.44 mg/dl) lower in the intervention group. After a follow-up of 2 years, there were no differences in mortality, CVD events or surrogate end points such as intima media thickness.

So in summary, the differences in effects on CV risk management and clinical outcome between the various studies may be explained by differences in patient characteristics, design, and follow-up.

The lack of effect on lifestyle-related aspects deserves some comment. Previous studies show benefit of a lifestyle intervention, when targeted at a single risk factor.[24–27] Recent reports involving multiple health behavior changes usually report no or limited effect.[28–31] Our results are in line with these studies. Also the Steno-2 study reported no beneficial effect on weight, smoking, or physical activity.[32] Only a few studies compared the effect of single vs. multiple interventions, all targeted at physical activity and nutrition.[33–35] Some showed superiority of a single intervention, whereas others showed better results with multiple interventions.[33–35] In a recent review, it was suggested that the number of choices in multiple interventions may overwhelm the patients.[36] This may be relevant in our study as well, because we have formulated 11 treatment targets for our patients.

Several other issues need to be discussed when considering the absence of a significant treatment effect in our study. First, at the start of the study, both patients and their physicians were informed about the existing guidelines, the goals and aim of the study. The quality of care in the control group also improved, as is evidenced by better BP and lipid management and the increased use of various medications (Figure 2). This phenomenon, which is known as contamination bias, has reduced the magnitude of the differences

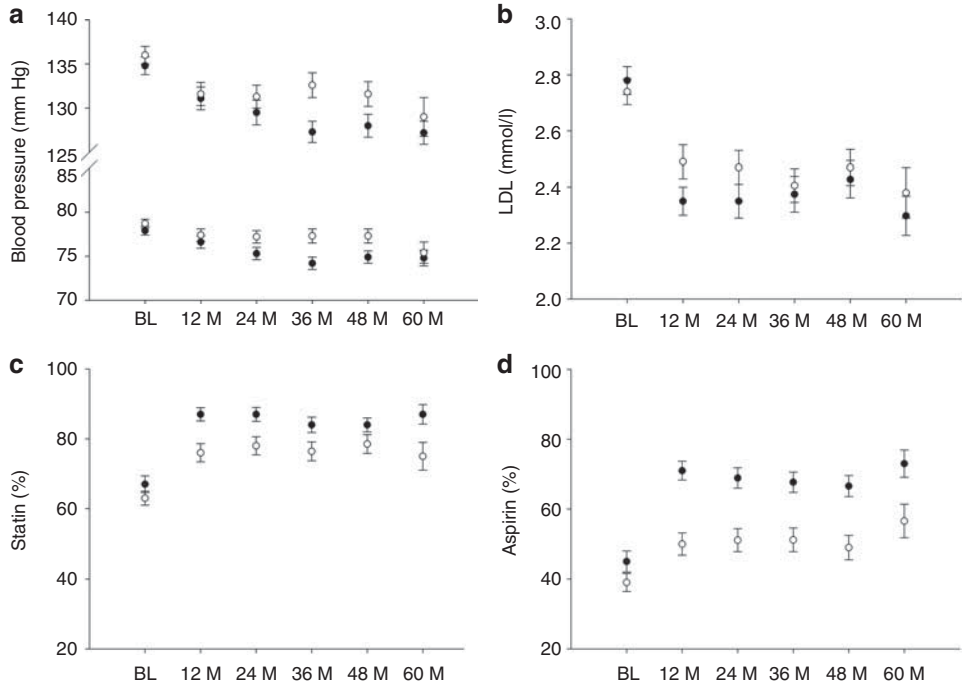


**Figure 2 | Change in oscillometric BP (a), LDL cholesterol (b), use of statins (c) and aspirin (among those not on oral anticoagulants at baseline) (d) in both the intervention (black symbols) and control group (white symbols) during the first 5 years of the trial.** *P*-value for difference between groups for systolic BP = 0.002; *P*-value for difference between groups for diastolic BP <0.001; *P*-value for difference between groups for LDL cholesterol = 0.008; *P*-value for difference between groups for statins = 0.002; *P*-value for difference between groups for aspirin <0.001; conversion factor to mg/dl: LDL cholesterol 38.6. BL, baseline; BP, blood pressure; LDL, low-density lipoprotein; M, months.

**Table 3 | Relative effects of strict implementation of the guidelines on all pre-specified primary and secondary outcomes**

| | Control | | Intervention | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Number of events | Person-years | Number of events | Person-years | *P*-value for difference | Hazard ratio[a] | Lower 95% CI | Upper 95% CI |
| Composite[b] | 42 | 1767 | 38 | 1787 | 0.63 | 0.90 | 0.58 | 1.39 |
| (Non) fatal AMI | 11 | 1797 | 12 | 1813 | 0.85 | 1.08 | 0.48 | 2.45 |
| (Non) fatal cerebrovascular disease | 15 | 1781 | 12 | 1805 | 0.54 | 0.79 | 0.37 | 1.69 |
| Fatal CV event | 25 | 1812 | 23 | 1830 | 0.75 | 0.91 | 0.51 | 1.61 |
| Ischemic stroke | 11 | 1782 | 9 | 1805 | 0.64 | 0.81 | 0.34 | 1.96 |
| All-cause mortality | 52 | 1812 | 46 | 1830 | 0.52 | 0.88 | 0.59 | 1.30 |
| ESRD | 59 | 1714 | 50 | 1746 | 0.32 | 0.83 | 0.57 | 1.20 |
| CABG | 11 | 1784 | 12 | 1804 | 0.86 | 1.08 | 0.48 | 2.44 |
| PTCA | 16 | 1772 | 21 | 1790 | 0.40 | 1.30 | 0.68 | 2.50 |
| Amputation | 4 | 1808 | 6 | 1822 | 0.53 | 1.49 | 0.42 | 5.29 |
| CHDplus[c] | 31 | 1743 | 36 | 1761 | 0.57 | 1.15 | 0.71 | 1.86 |

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CV, cardiovascular; ESRD, end-stage renal disease defined as transplantation or dialysis; CABG, coronary artery bypass grafting; CHDplus, coronary heart disease plus; PTCA, percutaneous coronary angioplasty.
[a]Based on unadjusted Cox proportional hazards models using intention-to-treat principle.
[b]Non-fatal AMI, non-fatal stroke, fatal CV event (whatever comes first).
[c]Non-fatal AMI, fatal coronary event, CABG, PTCA (whatever comes first).

between the two groups and therefore limits our ability to detect differences in events rates. On the basis of the meta-analyses on BP lowering and lipid lowering, a difference in systolic pressure of 3.0 mm Hg could result in a 6% reduction in coronary events, and a difference of 0.1 mmol/l in LDL in a 2% reduction of CVD events.[37,38] Our trial is not powered to detect such a small effect size. Yet, our 95% CI around the observed effect size includes this estimate (Table 3). We have not taken this contamination bias in to account in our power calculation.

Second, the incidence of the primary end point is somewhat lower than expected. This limits our ability to detect a difference between groups. In the recent Kidney Disease: Improving Global Outcomes CKD Prognosis Consortium analysis, the incidence of CVD events in our study is among the lowest of the 10 included cohorts.[39] Finally, recent studies have cast doubt on the efficacy of some of our interventions. There was no benefit of intensive BP or glucose lowering in otherwise reasonably well-controlled patients in recent trials.[40,41] As BP at baseline in our

study was (relatively) well controlled, the impact of a further lowering on outcome may be small. Taking all these factors mentioned above into account, one could argue that in retrospect our study turned out to be underpowered.

A final aspect needs to be mentioned. Although our study fails to show an improvement in CVD outcome, the support of the nurse practitioner results in equal and for some risk factors even better quality of care. Although the study was not specifically designed to assess cost effectiveness, it seems attractive to hypothesize that care in the intervention group is less costly. Indeed, CanPREVENT showed that nurse practitioner care was cost effective.[42] The results are therefore supportive to a view that nurse practitioner care (using strict guidelines and supervision) can substitute for specialist care. This is an important notion in view of the increasing incidence of patients with CKD, and deserves further attention.[43,44]

In conclusion, in this randomized study of 788 outpatients with CKD with mean follow-up of 4.6 years, intensive treatment with the aid of nurse practitioners resulted in better control of some risk factors, but did not reduce the incidence of myocardial infarction, ischemic stroke, or CVD death. Targeting multiple lifestyle changes was ineffective.

## MATERIALS AND METHODS

### Study design

MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) is a multi-center randomized controlled trial. Results are reported according to CONSORT guidelines.[45] The research protocol was approved by the local ethical committees and all participants gave written informed consent. Rationale and design have been published elsewhere.[16,46] In brief, subjects were recruited from outpatient nephrology clinics of nine Dutch hospitals that offered a full range of nephrology treatment including kidney replacement therapy. Patients were eligible for inclusion when diagnosed with moderate–to-severe CKD (estimated creatinine clearance by the Cockcroft–Gault equation between 20 and 70 ml/min).

Recruitment began in April 2004 and continued until December 2005.

Randomization to treatment was performed in a 1:1 ratio stratified by center and kidney transplant status using a Web-based block randomization module. All patients were subject to identical guidelines and treatment goals, which were described previously.[16] At baseline, information on medical history, physical activity, and medication use was obtained by questionnaire. Patients underwent a physical examination and urine and blood samples were taken. These measurements were repeated annually. Patients were asked to fill out a questionnaire on quality of life (SF-36 and EQ-5D) yearly. All laboratory measurements were performed in local laboratories.

The underlying diagnosis of kidney disease was determined by the treating physician using available history, clinical course, and histopathology (if available) and categorized using the ERA-EDTA (European Renal Association) registration criteria.

In patients with overt proteinuria, protein in urine was assessed in g per 24 h. However, by design in patients with known microalbuminuria albumin in urine was measured in mg per 24 h and protein in g per 24 h was not measured.

To obtain one value for proteinuria in all patients, albumin values were converted to proteinuria value using the same approach as applied by Kidney Disease: Improving Global Outcomes (i.e., by multiplying albumin values by 3/2).[39]

Both groups received an automated oscillometric BP measurement every 6 months.

In the intervention group, a nurse practitioner, supervised by a qualified nephrologist, actively pursued lifestyle intervention (physical activity, nutritional counseling, weight reduction, and smoking cessation), the use of specified mandatory medication (statin, either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, active vitamin D (alfacalcidol), and aspirin and the implementation of current guidelines (Supplementary Table S1 and S2 online). Modification of therapy was executed to achieve target values (Supplementary Table S1 online).

The approach and coaching by nurse practitioners has been described previously.[47] In their contacts with patients, nurse practitioners aimed at pursuing strict adherence to guidelines and modifying lifestyle by improving self-management by the patient.[48]

### Endpoints

Primary outcome was a composite of myocardial infarction, ischemic stroke, and CVD mortality. Myocardial infarction was defined as evident new ischemic changes on an electrocardiogram or an established rise and fall pattern of cardiac enzymes. Ischemic stroke was defined as characteristic clinical symptoms and evidence of recent cerebral ischemia using an appropriate imaging technique (computed tomography scan or magnetic resonance imaging). CVD mortality was defined as death because of myocardial infarction, ischemic stroke, ruptured abdominal aneurysm, terminal heart failure, or sudden death. An independent end point adjudication committee, blinded for group assignment, reviewed source documentation for all suspected primary end points and deaths. Secondary end points were vascular interventions, all-cause mortality, and start of kidney replacement therapy.

### Statistical analysis

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

All analyses were conducted according to the intention-to-treat principle. Effects of treatment on study end points were estimated as HRs and their corresponding 95% CIs with the use of unadjusted Cox proportional-hazard models, involving survival time to the first relevant end point in any individual patient. Data for patients were censored at their date of death, date of last visit (those alive at the end of follow-up), or date when last known to be alive (those with unknown vital status).

Differences in continuous and dichotomous variables between the two treatment groups during the follow-up period were estimated using linear mixed models (generalized estimating equations).[49] For that analysis, interest was in the mean difference over time in risk factor levels between treatment arms rather than the pattern of the change. Generalized estimating equation analyses were performed using on trial measurements with adjustments for baseline measurements. All *P*-values were two-sided, and *P*-values $<0.05$ implied statistical significance. No adjustment for multiple statistical testing was made.[50] The homogeneity of treatment effects across subgroups (none of which were pre-specified) was tested by

adding interaction terms to the relevant Cox models. All analyses were performed with the use of SPSS 17.0 (SPSS, Chicago, IL).

An independent data and safety monitoring committee reviewed the incidence of the primary end point in the two groups at regular 3-month intervals using group sequential analysis.[51] The sequential analysis has been detailed elsewhere.[16] The HR and its CI for the primary end point were adjusted for the cumulative testing and for the stratification factors.[51]

## DISCLOSURE

JFMW received lecture fees and travel reimbursements by Amgen and Genzyme. ADvZ received lecture fees and travel reimbursements by Genzyme. PJB received travel reimbursements by Amgen. The remaining authors declared no competing interests.

## ACKNOWLEDGMENTS

The MASTERPLAN Study was supported by grants from the Dutch Kidney Foundation (Nierstichting Nederland, number PV 01), and the Netherlands Heart Foundation (Nederlandse Hartstichting, number 2003 B261). Unrestricted grants were provided by Amgen, Genzyme, Pfizer, and Sanofi-Aventis.

### Data safety monitoring board

Members of the data safety and monitoring board were Dr Ingeborg van der Tweel (Department of Biostatistics, University Medical Centre Utrecht), Professor Dr JWM Lenders (Department of Internal Medicine, Radboud University Nijmegen Medical Centre), and Professor Dr TJ Rabelink, (Department of Nephrology, Leiden University Medical Centre).

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## SUPPLEMENTARY MATERIAL

**Figure S1.** The change in use of use of RAS-inhibitors (ACE/ARB) (top), active vitamin D (or analogs) (bottom) in both the intervention (black symbols) and control group (white symbols) during the first five years of the trial.

**Figure S2.** The change in body mass index (BMI) (top) and current smoking (bottom) in both the intervention (black symbols) and control group (white symbols) during the first five years of the trial.

**Table S1.** Risk factors that were intensively addressed by the nurse practitioner in the MASTERPLAN study.

**Table S2.** Standard medication to reduce cardiovascular risk in MASTERPLAN.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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