Nurse Practitioner Care Improves Renal Outcome in Patients with CKD


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ABSTRACT

Treatment goals for patients with CKD are often unrealized for many reasons, but support by nurse practitioners may improve risk factor levels in these patients. Here, we analyzed renal endpoints of the Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners (MASTERPLAN) study after extended follow-up to determine whether strict implementation of current CKD guidelines through the aid of nurse practitioners improves renal outcome. In total, 788 patients with moderate to severe CKD were randomized to receive nurse practitioner support added to physician care (intervention group) or physician care alone (control group). Median follow-up was 5.7 years. Renal outcome was a secondary endpoint of the MASTERPLAN study. We used a composite renal endpoint of death, ESRD, and 50% increase in serum creatinine. Event rates were compared with adjustment for baseline serum creatinine concentration and changes in estimated GFR were determined. During the randomized phase, there were small but significant differences between the groups in BP, proteinuria, LDL cholesterol, and use of aspirin, statins, active vitamin D, and antihypertensive medications, in favor of the intervention group. The intervention reduced the incidence of the composite renal endpoint by 20% (hazard ratio, 0.80; 95% confidence interval, 0.66 to 0.98; \(P=0.03\)). In the intervention group, the decrease in estimated GFR was 0.45 ml/min per 1.73 m\(^2\) per year less than in the control group (\(P=0.01\)). In conclusion, additional support by nurse practitioners attenuated the decline of kidney function and improved renal outcome in patients with CKD.


CKD is a growing public health problem worldwide. Patients with CKD are at risk of progression to ESRD, which is associated with considerable morbidity, mortality, diminished quality of life, and high health care costs. It is suggested that the development of ESRD can be prevented or delayed by early detection and treatment of CKD, and a multifactorial approach including BP control, reduction of proteinuria, lipid-lowering therapy, smoking cessation, improved glycemic control, and...
and weight reduction is advocated.\textsuperscript{4,5} CKD guidelines address these risk factors and treatment targets have been defined.\textsuperscript{3,6} Implementation of guidelines is rather difficult and it is well known that treatment goals are often not met.\textsuperscript{7–9} Coaching by nurse practitioners may be beneficial. Intensified intervention aimed at multiple risk factors implemented by nurse practitioners improved coronary risk factors in patients with coronary artery disease and after myocardial infarction.\textsuperscript{10,11} In patients with diabetes mellitus, a target-driven, multifactorial intervention improved risk factors and reduced the risk of cardiovascular and microvascular events.\textsuperscript{12,13} We recently showed that intensified support by nurse practitioners also improved risk factor levels in patients with CKD.\textsuperscript{14,15} However, the intervention did not significantly reduce the rate of cardiovascular events.\textsuperscript{15} In this analysis, we evaluated the effect of the intervention on renal endpoints after extended follow-up.

**RESULTS**

In total, 788 patients were included in our study, 395 of whom were randomized to the intervention group and 393 to the control group (Supplemental Figure 1). Baseline characteristics were balanced between the groups, apart from a history of cardiovascular disease, which was more common in the intervention group, and current smoking, which was less prevalent in the intervention group (Table 1). Median follow-up was 5.7 years.

**Effect of the Intervention on Risk Factor Levels and Medication Use**

Mean risk factor levels and medication use in the intervention and control groups during the randomized phase of the study are shown in Table 2.

Several risk factor levels improved in both the intervention and control groups. In addition, medication use increased in both groups. Compared with the control group, the intervention group had a lower BP, proteinuria, and LDL cholesterol, and more frequently used aspirin, statins, active vitamin D, and angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) (Supplemental Table 1, Table 2).

**Effect of the Intervention on Renal Endpoints**

The intervention reduced the incidence of the composite outcome (hazard ratio [HR], 0.80; 95% confidence interval [95% CI], 0.66 to 0.98; \(P=0.03\)) (Figure 1). We used a 50% increase in serum creatinine as an endpoint irrespective of the subsequent course. This definition includes transient increases in serum creatinine concentration. However, using other definitions for this endpoint, the differences between the intervention and control groups persisted (Supplemental Table 2). The intervention did not significantly lower the rate of the individual components (Supplemental Figure 2, Table 3). We calculated the rate of estimated GFR (eGFR) decline using a median of 19 data points (range, 2–23) per patient. The rate of eGFR decline was significantly lower in the intervention group (\(P=0.01\)) (Table 3). An

### Table 1. Baseline characteristics of the MASTERPLAN study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group (n=395)</th>
<th>Control Group (n=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.9±13.1</td>
<td>59.3±12.8</td>
</tr>
<tr>
<td>Men</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Nephrologic diagnosis\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Renovascular</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>GN</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Intestinal nephritis</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Congenital</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Unknown</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Kidney transplant recipient</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>History of diabetes mellitus\textsuperscript{b}</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Prior cardiovascular disease\textsuperscript{c}</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m\textsuperscript{d})</td>
<td>35.9±14.2</td>
<td>35.2±12.9</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)\textsuperscript{e}</td>
<td>2.05±0.81</td>
<td>2.05±0.79</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>138±20</td>
<td>139±22</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80±11</td>
<td>81±11</td>
</tr>
<tr>
<td>Protein creatinine ratio (mg/g)\textsuperscript{f}</td>
<td>149 (41–632)</td>
<td>193 (38–742)</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.0±0.4</td>
<td>4.0±0.4</td>
</tr>
<tr>
<td>Fasting LDL cholesterol (mg/dl)\textsuperscript{g}</td>
<td>107±37</td>
<td>106±35</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)\textsuperscript{h}</td>
<td>13.2±1.6</td>
<td>13.2±1.6</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.1±0.9</td>
<td>6.1±0.9</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)\textsuperscript{i}</td>
<td>9.56±0.60</td>
<td>9.48±0.56</td>
</tr>
<tr>
<td>Phosphate (mg/dl)\textsuperscript{j}</td>
<td>3.44±0.77</td>
<td>3.41±0.77</td>
</tr>
<tr>
<td>PTH (pg/ml)\textsuperscript{k}</td>
<td>80 (47–135)</td>
<td>82 (49–127)</td>
</tr>
<tr>
<td>Sodium intake (g/24 h)\textsuperscript{l}</td>
<td>3.6±1.4</td>
<td>3.6±1.4</td>
</tr>
<tr>
<td>Body mass index (kg/m\textsuperscript{2})</td>
<td>27.0±4.6</td>
<td>27.2±4.9</td>
</tr>
<tr>
<td>Smoking</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Physical activity guideline adherence</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>Oral anticoagulant drug use</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Aspirin use\textsuperscript{m}</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Statin use</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Active vitamin D use</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>81</td>
<td>78</td>
</tr>
<tr>
<td>Antihypertensive drugs (n)</td>
<td>2.4±1.3</td>
<td>2.4±1.4</td>
</tr>
</tbody>
</table>

Data are given as mean±SD, percentage, or median (interquartile range). PTH, parathyroid hormone.

\textsuperscript{a}The underlying diagnosis of kidney disease was determined by the treating physician using available history, clinical course, and histopathology (if available).\textsuperscript{15}

\textsuperscript{b}Diabetes mellitus is defined as using blood glucose lowering medication or fasting glucose >7.0 mmol/L.

\textsuperscript{c}Cardiovascular disease is defined as myocardial infarction, stroke, or vascular intervention.

\textsuperscript{d}Using the MDRD equation reexpressed for standardized serum creatinine.

\textsuperscript{e}To convert serum creatinine to \(\mu\)mol/L, multiply by 88.4.

\textsuperscript{f}To convert protein creatinine ratio to mg/mmol, multiply by 0.113.

\textsuperscript{g}To convert LDL cholesterol to mmol/L, multiply by 0.259.

\textsuperscript{h}To convert hemoglobin to mmol/L, multiply by 0.9.

\textsuperscript{i}To convert phosphate to mmol/L, multiply by 0.323.

\textsuperscript{j}To convert PTH to pmol/L, multiply by 0.11.

\textsuperscript{k}To convert sodium intake to mmol/24 h, multiply by 43.5.

\textsuperscript{m}In those not using oral anticoagulant drugs.
additional analysis, using only annual creatinine values, did not change the main findings (data not shown).

Although there was no conclusive evidence for violation of the proportional hazards assumption (by log-log plots and Schoenfeld test, data not shown), Figure 1 shows that the benefits of the intervention became evident after 2 years of follow-up. Therefore, we performed additional analyses by an extended Cox model including a Heaviside function with a knot at 2 years of follow-up. Table 4 shows that there was no significant difference between the intervention and control groups within the first 2 years of follow-up. After 2 years, however, there was a significant effect of the intervention on the composite outcome, and the individual components of ESRD and a 50% increase in serum creatinine. Mortality was not affected by the intervention. Extended follow-up data were included in the analyses presented in Table 4. We performed additional analyses without the data collected during extended follow-up. The results were comparable with those presented in Table 4 (data not shown).

**Number of Visits**
The mean number of outpatient clinic visits (physician and/or nurse practitioner) during the first 2 years of the study was significantly higher in the intervention group than in the control group (7.2 versus 4.7 visits per year; \(P<0.001\)). The mean number of physician visits in the intervention group was significantly lower than in the control group (2.8 versus 3.7 visits per year; \(P<0.001\)).

![Figure 1](https://www.jasn.org)
period from 2008 to 2009). Physicians spent their usual follow-up visit time (10–15 minutes per visit).

DISCUSSION

In this study, we show that additional support by nurse practitioners in CKD patients attenuated the decline of kidney function and improved renal outcome. These benefits became notable after 2 years of follow-up.

The study results are very important. First, the ability to postpone start of renal replacement therapy has a major effect on patients’ quality of life and it may have substantial budgetary consequences. Second, the data indicate that the clinical care for the growing population of CKD patients may not depend on nephrologists alone.

We recently reported the main outcome of our randomized trial.15 After a follow-up of 4.6 years, there were no significant differences in cardiovascular outcome (HR, 0.90; 95% CI, 0.58 to 1.39) nor in the incidence of ESRD (HR, 0.83; 95% CI, 0.57 to 1.20). This study shows that the effects of the intervention on renal endpoints became evident with longer follow-up. This is a general observation in other large randomized trials and underlines the importance of long-term follow-up of interventions that aim at slowing progression of CKD.12,16–18

Few randomized controlled trials have studied CKD progression and most have evaluated the effect of a single target intervention. Our findings support the hypothesis that a multifactorial intervention directed at multiple treatment targets is effective even when achieving only modest improvements.

We observed differences in systolic and diastolic BP, proteinuria, LDL cholesterol, and the use of aspirin, statins, active vitamin D, and ACEIs/ARBs. Our study does not allow us to draw conclusions on the role of the separate risk factors and drugs in the efficacy of the intervention. Still, on the basis of recent evidence, we propose that the reduction in renal endpoints is mainly related to improved BP control, the increased use of ACEIs/ARBs, the reduction of proteinuria, and possibly the increased use of active vitamin D.

First, the role of BP in progressive kidney disease has been firmly established.19 Several studies have shown a beneficial effect of a lower BP target on progression of CKD.16,18,20 Importantly, in most studies, the effect of an initial reduction of BP became evident only after long-term follow-up.16,18 In our study, mean BPs in the intervention group were reduced by 4 mmHg systolic and 2 mmHg diastolic after 1 year, and by 5 mmHg systolic and 3 mmHg diastolic after 2 years compared with the control group. On the basis of the aforementioned studies, we consider it likely that such differences in BP at least partly explained the differences in renal outcome.

Table 3. Event rates of renal endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Intervention Group (n=395)</th>
<th>Control Group (n=393)</th>
<th>HR 95% CI P Value</th>
<th>HR 95% CI P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death, ESRD,* or 50% increase in serum creatinine</td>
<td>180 99.6</td>
<td>208 118.7</td>
<td>0.80b 0.66 to 0.98 0.03</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>68 32.7</td>
<td>74 36.8</td>
<td>0.85b 0.62 to 1.18 0.34</td>
<td></td>
</tr>
<tr>
<td>Death before ESRD</td>
<td>50 24.4</td>
<td>55 27.8</td>
<td>0.87b 0.59 to 1.27 0.47</td>
<td></td>
</tr>
<tr>
<td>ESRDb</td>
<td>77 37.4</td>
<td>89 44.8</td>
<td>0.75b 0.52 to 1.08 0.12</td>
<td></td>
</tr>
<tr>
<td>50% increase in serum creatininec,d</td>
<td>130 71.9</td>
<td>153 87.3</td>
<td>0.81b 0.64 to 1.03 0.09</td>
<td></td>
</tr>
<tr>
<td>eGFR decline (ml/min 1.73 m² per year)</td>
<td>1.26 (SEM 0.12)</td>
<td>1.71 (SEM 0.12)</td>
<td>0.45* 0.12 to 0.78 0.01</td>
<td></td>
</tr>
</tbody>
</table>

*ESRD is defined as initiation of chronic dialysis or kidney transplantation.
*bHRs, adjusted for baseline serum creatinine concentration.
*cDeath is considered competing.
*dIncluding ESRD.
*eEstimated difference mean eGFR decline, studied by a linear mixed model. Data points after the start of chronic dialysis or kidney transplantation were not included in the analysis.

Table 4. Effect of the intervention on renal endpoints within 2 years of follow-up and after 2 years of follow-up

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Follow-Up Time ≤2 yr</th>
<th>Follow-Up Time ≥2 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death, ESRD,* and 50% increase in serum creatinine</td>
<td>1.31 0.91 to 1.88 0.14</td>
<td>0.64 0.50 to 0.82 &lt;0.001</td>
</tr>
<tr>
<td>Death before ESRD</td>
<td>0.92 0.42 to 2.02 0.84</td>
<td>0.86 0.56 to 1.32 0.48</td>
</tr>
<tr>
<td>ESRDb</td>
<td>1.61 0.76 to 3.41 0.21</td>
<td>0.37 0.16 to 0.85 0.02</td>
</tr>
<tr>
<td>50% increase in serum creatinineb,c</td>
<td>1.48 0.97 to 2.26 0.07</td>
<td>0.62 0.46 to 0.83 0.001</td>
</tr>
</tbody>
</table>

HRs, adjusted for baseline serum creatinine concentration, compared with the control group, using an extended Cox model including a Heaviside function with a knot at 2 years of follow-up.

*ESRD is defined as initiation of chronic dialysis or kidney transplantation.
*bDeath is considered competing.
*cIncluding ESRD.
There is good evidence that ACEIs or ARBs slow progression of kidney disease by mechanisms beyond decreasing BP.\textsuperscript{19,21,22} More patients in the intervention group used ACEIs or ARBs. Therefore, ACEI/ARB use may have been a contributing factor to the beneficial effect of the intervention.

A low vitamin D level is associated with progression of CKD.\textsuperscript{23} In a randomized study, the vitamin D analog paricalcitol lowered albuminuria in patients with diabetic nephropathy.\textsuperscript{24} It is thus tempting to speculate that increased active vitamin D use may have contributed to the improved outcome in the intervention group. Admittedly, evidence from randomized clinical trials that vitamin D supplementation retards CKD progression is lacking.

In the general population, as well as in high-risk cohorts, even small variation in albuminuria is associated with significant differences in ESRD risk.\textsuperscript{25} In CKD patients, the level of albuminuria is related to ESRD.\textsuperscript{26} Although the difference in proteinuria between the Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners (MASTERPLAN) intervention and control groups was small, we think it may have contributed to the beneficial effect of the intervention.

It is unlikely that aspirin use explained the improved renal outcome in the MASTERPLAN intervention group, because aspirin use did not affect renal function in patients with hypertension and CKD.\textsuperscript{27}

LDL cholesterol level and statin use are also unlikely explanatory factors. In the Study of Heart and Renal Protection, renal disease progression was not reduced by using simvastatin plus ezetimibe compared with placebo, despite a larger reduction in LDL cholesterol compared with the MASTERPLAN study.\textsuperscript{28} Stricter control of diabetes is associated with a lower rate of GFR decline in the long term.\textsuperscript{27} This does, however, not apply to our study, because we observed no difference in hemoglobin A1c between the intervention and control groups, both in the total population and the subpopulation of patients with diabetes (data not shown).

We cannot exclude that other unmeasured factors contributed to the efficacy of the intervention. Moreover, there are also unmeasured effects of nurse practitioner care. Nurse practitioners spent more time than physicians treating and educating their patients. This included not only visits to the outpatient clinic\textsuperscript{15} but also contact by telephone or Email. Nurses probably made an effort to adjust to patients’ schedules and it is likely that a patient could more easily contact a nurse practitioner than a physician. This may have led to earlier detection of (potential) problems and earlier interventions, such as adjustment of medication resulting in reduced use of nonsteroidal anti-inflammatory drugs, fewer episodes of AKI, less medication errors, or fewer days in hospital. Unfortunately, such data are not available.

### Studies on the Value of Nurse Practitioner Care

The value of nurse practitioner care in chronic disease has been investigated in other fields of medicine, especially in diabetes mellitus\textsuperscript{12,13} and coronary heart disease.\textsuperscript{10,11,29} However, few studies reported the effect of a multifactorial intervention on "hard" endpoints. In the Steno-2 study, an intensified intervention aimed at multiple risk factors particularly affected BP control, glucose and lipid regulation, and albuminuria in patients with type 2 diabetes. No differences were observed in body mass index, smoking, and activity level.\textsuperscript{12} The authors were unable to identify which treatment component was most crucial in reducing the incidence of diabetes-related complications. A possible contribution of unmeasured effects of the intervention was not mentioned\textsuperscript{12} and probably not considered in view of the large differences in BP, LDL cholesterol, and ACEI and statin use. The Global Secondary Prevention Strategies to Limit Event Recurrence after Myocardial Infarction study showed that the rate of several cardiovascular endpoints was reduced by a multifactorial intervention by a cardiac rehabilitation team, including a specialized nurse. The intervention significantly affected several (lifestyle-related) risk factors and medication use.\textsuperscript{29} However, only small differences compared with the control group were observed. For instance, differences in LDL cholesterol and ACEI use were smaller than in MASTERPLAN. Therefore, as in our study, a contribution of unmeasured effects of the intervention on endpoints seems likely. The effect of nurse practitioner care in CKD was studied in a Canadian trial.\textsuperscript{30,31} In contrast to the MASTERPLAN study, the Canadian Prevention of Renal and Cardiovascular Endpoints Trial (CanPREVENT) did not show that nurse-coordinated care improved the rate of GFR decline or control of most risk factors compared with usual care.\textsuperscript{30} Patients in the CanPREVENT study largely had nonprogressive kidney disease and follow-up time was short. However, nurse-coordinated care entailed several benefits. For instance, patients participated in weight loss programs and visited a dietician more often, there were fewer visits to specialists such as cardiologists, and, most importantly, patients in the intervention group spent fewer days in hospital.\textsuperscript{31} As a result, the CanPREVENT study showed that nurse practitioner care was cost-effective.\textsuperscript{31}

### Estimation of Savings and Costs

The MASTERPLAN study was not designed to include a formal cost-benefit analysis and this was not the focus of our manuscript. However, a crude estimate of savings and costs suggests that our intervention is cost-beneficial. Details of our calculations are provided in the Supplemental Material.

### Strengths and Limitations of Our Study

Our study was randomized and all analyses were based on intention to treat. Another strength of our study is the extended follow-up. The data collected during the extended follow-up period were very important in our analyses. Unfortunately, we have no data on BP (and other risk factor levels) after end of the active study period. However, it is likely, as was observed before,\textsuperscript{18} that BP differences will have disappeared with more prolonged follow-up.
We only observed modest differences in risk factor levels between the two groups in the study period. This can be explained because our patients were quite well controlled at baseline. For instance, most patients met the BP treatment goal and ACEI/ARB use was already very high at baseline. Moreover, quality of care also improved in the control group, which was attributed to contamination bias, as discussed elsewhere.\textsuperscript{15} Admittedly, the use of ESRD, which is defined as the need for renal replacement therapy, as an endpoint can be criticized because the choice to start dialysis or perform a kidney transplant is not objective and is influenced by complaints and quality of life. However, our conclusions are supported by the observed differences in objective renal endpoints (\textit{i.e.}, a 50% increase in serum creatinine concentration and decline of eGFR).

The generalizability of our results may be limited by the selection of relatively young and “healthy” CKD patients. Not only were risk factor levels already quite well controlled at baseline (as mentioned before), also the incidence of cardiovascular events was lower than expected.\textsuperscript{15}

In conclusion, our data provide evidence that intensified support by nurse practitioners attenuates the decline of kidney function and improves renal outcome in patients with prevalent CKD.

**CONCISE METHODS**

**Study Design**

The MASTERPLAN study (ISRCTN registry number 73187232) is a randomized controlled trial conducted in nine centers with a nephrology department in The Netherlands. Rationale, design, and main outcome have been reported elsewhere.\textsuperscript{15,32,33} In brief, adult patients with moderate to severe CKD (estimated creatinine clearance by the Cockcroft–Gault equation between 20 and 70 ml/min per 1.73 m\textsuperscript{2}) were eligible for inclusion.\textsuperscript{33} Exclusion criteria were as follows: a renal transplant <1 year before inclusion, ARF or rapidly progressive GN established by the treating physician, any malignancy <5 years before inclusion other than basocellular or squamous cell carcinoma of the skin, participation in other clinical trials requiring the use of study medication. Ethics committee approval was obtained as well as written informed consent from all participants. Between April 2004 and December 2005, patients were enrolled.

At baseline, information on medical history, physical activity, and medication use was obtained. Patients also underwent a physical examination and urine and blood samples were taken. After the baseline evaluation, patients were randomized to receive nurse practitioner support added to specialist physician care (intervention group) or specialist physician care alone (control group). Randomization to treatment was stratified by center and renal transplant status using a web-based randomization module and performed in predefined blocks. The same set of guidelines and treatment goals applied to all patients (Supplemental Table 3). 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, and the implementation of current guidelines.\textsuperscript{15,34} Motivational interviewing and coaching to improve self-management by the patient were key elements in the role of nurse practitioners.\textsuperscript{34} Medication was prescribed by the supervising nephrologist at the request of the nurse practitioner. In the control group, specialist physician care comprised “usual care” according to CKD guidelines.\textsuperscript{3,6} In contrast to the intervention group and in agreement with real-life practice, no extra measures were taken to insure adherence to these guidelines in the control group.

Patients in the intervention group received follow-up by the nurse practitioner as often as considered necessary. Study laboratory evaluation, office BP measurements, and evaluation of medication use were performed at least quarterly. Annually more extensive study laboratory measurements were performed and the patients filled out questionnaires. Patients in the control group also visited the clinic every year to undergo a series of study measurements and fill out questionnaires. The frequency of visits in the control group was up to the treating physician, representing usual care. For the period between the annual study visits, clinical data, including laboratory measurements, were derived from the medical records of patients in the control group.

**Extended Follow-Up**

The MASTERPLAN study was closed in July 2010. After study closure, patients were treated according to local practice. After July 2010, in most hospitals both patients from the intervention group and patients from the control group received nurse practitioner care. We extended follow-up for the current analyses. We retrieved data on mortality and renal outcome parameters from the participating centers. The extended follow-up was closed in August 2011.

**Risk Factor Levels and Medication Use**

Differences in risk factor levels and medication use during follow-up were assessed. Risk factor values and medication use were no longer included in analyses from the moment that a patient reached a renal endpoint.

In patients with microalbuminuria, albuminuria data were converted to proteinuria data using the approach as applied by Kidney Disease Improving Global Outcomes (\textit{i.e.}, by multiplying albuminuria values by 1.5).\textsuperscript{15,26} We report protein creatinine ratio to correct for collection errors in 24-hour urine samples.

**Endpoints**

The primary outcome of the MASTERPLAN study was a composite of myocardial infarction, stroke, and cardiovascular mortality.\textsuperscript{15} In our secondary analysis, we evaluated several renal endpoints. We used a composite renal endpoint of death, ESRD, and 50% increase in serum creatinine. Death before ESRD was included in the composite endpoint because it is a competing risk factor for kidney failure.\textsuperscript{16} ESRD was defined as initiation of chronic dialysis or kidney transplantation. In addition, the three components of the composite renal endpoint were evaluated separately.

Another renal endpoint we used was the change in serum creatinine–based eGFR. During follow-up some hospitals changed their creatinine assay from a Jaffé to an enzymatic method. To take
this transition into account, creatinine values obtained with the Jaffé method were recalculated to reflect enzymatic values. Calibration equations were provided by the individual hospitals. Because enzymatic creatinine values were available, we used the Modification of Diet in Renal Disease (MDRD) study equation reexpressed for standardized serum creatinine to estimate GFR. To calculate the rate of change in eGFR, all available data points in a given patient were used. Data points after the start of chronic dialysis or kidney transplantation were not included in the analysis.

**Statistical Analyses**

All analyses were conducted according to the intention-to-treat principle. For descriptive statistics, continuous variables were expressed as the mean±SD for normally distributed data or as the median (interquartile range) for skewed data. Frequencies were expressed as proportions.

Improvement in risk factor levels and medication use in the intervention group during the randomized phase of the study was compared with the control group using independent-samples t tests, comparing the time average values using areas under the curves. For not normally distributed variables, the natural logarithm of variable values was used in the analysis.

We calculated the cumulative incidence of the composite endpoint using Kaplan–Meier curves. The effect of the intervention on the composite renal endpoint was studied using a Cox proportional hazards model adjusted for baseline serum creatinine. Similar models were also used to evaluate the effect on mortality, ESRD, and 50% increase in serum creatinine separately. If no endpoint occurred, data were censored at the date of the patient’s last follow-up moment. The proportional hazards assumption was checked with log-log plots and chi-squared test based on Schoenfeld residuals.

We used an extended Cox model including a Heaviside function with a knot at 2 years of follow-up and adjusted for baseline serum creatinine to obtain two different HRs for the first two years of follow-up, and subsequent follow-up, separately (post hoc analysis). We performed this post hoc analysis because the slopes of the curves shown in Figure 1 change at about 2 years of follow-up. After this, the incidence curves separate in favor of the intervention group. In addition, the MDRD study showed that within the first 2 years of follow-up, there was no significant effect of their intervention on endpoints.

Rate of change in eGFR was evaluated with a linear mixed effects model, with random intercepts and slopes. A product term (treatment × time) was included to ascertain the (fixed) rate of change between the treatment arms.

Data were analyzed without imputation. All P values were two-sided, and for all tests P values <0.05 were considered to indicate statistical significance. Analyses were performed with SPSS 16.0 (SPSS, Inc., Chicago, IL) or Stata 10.1 (StataCorp LP, College Station, TX) software.

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**REFERENCES**


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