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ORIGINAL RESEARCH ARTICLE

# Adherence to Renal Function Monitoring Guidelines in Patients Starting Antihypertensive Therapy with Diuretics and RAAS Inhibitors: A Retrospective Cohort Study

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**Abstract**

*Background* Acute kidney injury (AKI) might complicate antihypertensive therapy. In The Netherlands, general practitioner clinical practice guidelines provide clear recommendations on monitoring of renal function to minimize this risk. Our objective was to investigate how day-to-day clinical practice corresponds to the guidelines.

*Methods* We conducted a retrospective cohort study in a dynamic population, using data on >9,000 adults that was retrieved from the Integrated Primary Care Information database. We investigated whether serum creatinine (SCR) was measured within 30 and 365 days after the start of (combined) use of a diuretic, an angiotensin-converting enzyme inhibitor, and/or angiotensin receptor blocker. We also investigated the association between calendar year, sex, type of therapy, risk factors for AKI and practice and SCR measurement.

*Results* Of 6,593 subjects who met the study criteria for single drug therapy, SCR was measured in 1,233 subjects within 30 days and in 3,896 subjects within 365 days. For combined drug therapy recipients ($n = 2{,}497$), these were 545 and 1,687, respectively. Associated cumulative probabilities were 19 % and 66 % with single drug therapy, and 22 % and 74 % with combined drug therapy. Significant differences were observed between practices. SCR measurement was associated with other characteristics, except for sex. Within 365 days, SCR increased >30 % of baseline in 103 subjects (1.6 %) after the start of single drug therapy, and in 85 (3.4 %) subjects who initiated combined drug therapy. In the majority (>70 %) of these subjects, this did not result in subsequent monitoring or adjustment of antihypertensive treatment.

*Conclusions* Results from this study suggest that, on average, renal function is not monitored as strictly as recommended by relevant clinical practice guidelines.

**Key Points**

In the majority (>75 %) of subjects, renal function is not monitored during the first 30 days after the start of (combined) antihypertensive therapy with diuretics and/or renin–angiotensin–aldosterone system inhibitors (RASIs) in contrast to recommendations of the guidelines.

There is large variability between general practitioner practices with respect to renal function monitoring.

In our study population that comprises subjects without additional risk factors for the renal-impaired population, the incidence of renal impairment (increase in serum creatinine measurement >30 % of baseline) during the first 365 days after treatment initiation is relatively low (2.6–3.4 %), and did not lead to subsequent actions in the majority (>70 %) of subjects.

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## 1 Background

Lowering blood pressure reduces progression of chronic kidney disease (CKD) [1], but may also be associated with an increased risk of acute kidney injury (AKI) resulting from a disturbed autoregulation of the renin–angiotensin–aldosterone system (RAAS) caused by angiotensin-converting enzyme inhibitors (ACEIs) [4] or angiotensin receptor blockers (ARBs) [5], or due to volume depletion caused by diuretics [2]. This is illustrated by results from the CHARM trial where doubling of serum creatinine (SCR) and study medication discontinuation, due to SCR elevation, occurred significantly more often in the ARB-treated group than in the placebo group [3]. Certain medication combinations might be more harmful, as illustrated by the ONTARGET trial where combined drug therapy with an ACEI and an ARB increased the risk of renal impairment without an increase in benefit [4]. Another recent study found a 31 % higher risk of AKI with a triple-medication combination, consisting of non-steroidal anti-inflammatory drugs (NSAIDs) in combination with a diuretic plus an ACEI or ARB. The highest risk was observed in the first 30 days of use, and a trend toward an increased risk was observed for double medication combinations, including an NSAID in combination with a diuretic, ACEI, or ARB [5].

Risk minimization through monitoring of renal function is recommended in clinical guidelines, with subtle differences in timing, duration and frequency of monitoring, as well as with regard to changes of renal function that are considered as acceptable. The National Institute for Health and Care Excellence (NICE) clinical guideline on CKD recommends monitoring of renal function through SCR between 1 and 2 weeks after initiation or dose increase of ACEIs or ARBs. A $\leq$25 % decrease in estimated glomerular filtration rate (eGFR) or $\leq$30 % increase in SCR relative to baseline is accepted [6]. Dutch general practitioner (GP) clinical guidelines are stricter, and recommendations also relate to diuretics and not only recommend SCR measurements upon treatment initiation but also SCR measurements between 3 and 6 months after introduction or change of therapy and yearly thereafter [7].

Monitoring of renal function in relation to antihypertensive therapy has been investigated in a number of studies [8–17], but data on monitoring during the first 30 days of use—the period with the highest risk of AKI—as well as data on the incidence of abnormal renal function during monitoring are limited. Also, possible differences by GP practice have not been evaluated thus far.

The objective of this study was to investigate whether monitoring of renal function, during initiation of diuretics, ACEIs or ARBs by GPs is in line with the recommendations, as issued by the Dutch College of General Practitioners [7].

## 2 Methods

### 2.1 Study Design and Setting

We performed a retrospective cohort study, using data retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal, observational, dynamic database which contains the electronic medical records of a group of more than 600 GPs in The Netherlands. In the Dutch healthcare system, the GP plays a pivotal role and acts as a gatekeeper of medical care and information. Almost all inhabitants of The Netherlands are registered with a GP, independent of their health status. Details of the IPCI database have been described elsewhere [18, 19]. Briefly, the database contains the complete electronic medical records of approximately 1,000,000 subjects. These records contain anonymous longitudinal data on demographics, symptoms and diagnoses (coded in International Classification of Primary Care [ICPC] codes, and in free text), referrals, laboratory findings, hospitalizations, discharge letters, and medication prescriptions (including indication and dosage regimen). To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records in addition to the electronic medical records. The system complies with EU guidelines on the use of data for medical research and has been proven valid for pharmacoepidemiologic studies [19]. The Scientific and Ethical Advisory Board of the IPCI project approved the study.

### 2.2 Participants

The source population comprised all individuals who were registered with their GP for at least 365 days. The study period started on 1 January 2005 and ended on 31 December 2011. Subjects were followed until death, transfer out of practice, last data draw-down, or end of the study period, whichever came first.

### 2.3 Study Population

From the source population, two exposure cohorts were defined, i.e. a single-therapy cohort and a combined-therapy cohort. The single-therapy cohort consisted of patients aged $\geq$40 years who received a new (incident) medication prescription with a chemical substance from one of the Anatomical Therapeutic Chemical (ATC) classes 'C03' (diuretics), 'C09A' (ACEI) or 'C09C' (ARB) as single

therapy. Incident use meant that the patient had not used any of these ATC classes in the year before. The combined therapy cohort consisted of subjects aged ≥40 years who were already exposed to one of these ATC classes and started new use of a drug from another ATC class, as mentioned above, during follow-up.

The first date of medication prescription that led to inclusion of a subject in the study population of single drug therapy or combined drug therapy is referred to as the 'index date'. For both exposure cohorts, the new medication prescription had to be refilled at least once within 90 days of the first prescription to avoid misclassification of incidental use as chronic therapy. For combined drug therapy, the other medication(s) to which a subject was already exposed had to be refilled at least once during the first period of exposure to the new medication to exclude a switch in therapy.

In the Dutch healthcare system, GPs might continue therapy that is initiated by a specialist. For these patients, if monitoring of renal function is performed by the specialist, SCR measurements might be missing in the database. To include only patients for whom the therapy was initiated by the GP, we excluded patients with heart failure prior to the index date based on disease codes 'K77' (heart failure), 'K82' (cor pulmonale) and free text 'heart failure' and 'cardiac decompensation' in the medical record. In addition, subjects who met the criteria for referral to the nephrologist prior to the index date were excluded, being macro-albuminuria in combination with any eGFR, micro-albuminuria with an eGFR <30 ml/min/1.73 $m^2$ in subjects <65 years, or eGFR <45 ml/min/1.73 $m^2$ in subjects ≥65 years, or without information on eGFR within the year prior to the index date. Finally, patients in those cases where the indication for antihypertensive therapy at the index date was missing or different from hypertension were excluded, based on disease codes 'K85' (elevated blood pressure), 'K86' (hypertension uncomplicated), or 'K87' (hypertension complicated).

### 2.4 Outcome

The outcome of this study was the presence of an SCR measurement performed by the GP within 30 days, and within 365 days following the index date. We also investigated how SCR evolved during the 365 days following the index date, and whether an SCR increase >30 % of baseline resulted in subsequent monitoring or adjustment of antihypertensive treatment.

### 2.5 Covariables

In this study, we studied the influence of the following variables on renal function monitoring after index date: calendar year; age; sex; concomitant use of NSAIDs and/or high dose (>300 mg/day) of acetylsalicylic acid (ASA); diabetes mellitus (DM), based on prescription from the ATC class 'A10' (drugs used in diabetes) [20, 21]; and eGFR, which was obtained from the last available SCR measurement within the year prior to index date, using the equation published by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration [22]. We used eGFR categories as provided by the Kidney Disease Improving Global Outcomes (KDIGO) foundation: G1 'normal or high' ≥90; G2 'mildly decreased' 60–89; G3a 'mildly to moderately decreased' 45–59; G3b 'moderately to severely decreased' 30–44 ml/min/1.73 $m^2$ [23].

### 2.6 Statistical Analysis

For univariable analyses we calculated cumulative survival probabilities. We used Cox proportional hazards regression analysis for multivariable analyses, using GP practice as a stratification variable. We tested for interaction between baseline characteristics, and included interaction terms with a $p$-value of <0.05. We constructed survival plots and log(-log(survival)) versus log(time) plots for each baseline covariable to investigate deviation from proportionality. If indicated by these plots, hazard rates varying with time were modelled. Analyses that were performed to investigate GP practice differences only included GP practice as a multilevel categorical variable. Baseline characteristics of single and combined drug therapy were compared with Student's $t$-test and Pearson's Chi-square tests. All analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

## 3 Results

The source population consisted of 984,047 subjects with a valid history of at least 365 days in the IPCI database. After application of inclusion and exclusion criteria, 6,593 subjects were enclosed in the single drug study population and 2,497 subjects in the combined drug study population. In comparison to single drug therapy, combined drug therapy included older subjects (mean age 64.4 vs. 61.9 years; $p < 0.001$), a larger proportion of females (53.7 vs. 51.1 %; $p = 0.032$), and more subjects with DM (20.4 vs. 17.8 %; $p = 0.004$), whereas eGFR (78.0 vs. 77.8 ml/min/1.73 $m^2$; $p = 0.559$) and the proportion of NSAIDs at the start of therapy (0.4 vs. 0.5 %; $p = 0.336$) were comparable between groups. Detailed baseline characteristics are described in Table 1.

For single-medication use, 1,233 subjects had one or more SCR measurement within 30 days after the start of treatment, and 3,896 subjects had at least one SCR

**Table 1** Study cohort characteristics

| Characteristics | Single drug therapy [$N = 6,593$] $n$ (%) | Combined drug therapy [$N = 2,497$)] $n$ (%) |
|---|---|---|
| Males | 3,222 (49) | 1,157 (46) |
| Age category, years | | |
| 40–49 | 1,086 (16) | 288 (12) |
| 50–59 | 1,861 (28) | 603 (24) |
| 60–69 | 2,032 (31) | 788 (32) |
| 70–79 | 1,213 (18) | 590 (24) |
| 80+ | 401 (6) | 228 (9) |
| Calendar year at start of treatment | | |
| 2005 | 38 (1) | 8 (0) |
| 2006 | 168 (3) | 34 (1) |
| 2007 | 402 (6) | 116 (5) |
| 2008 | 906 (14) | 372 (15) |
| 2009 | 1,641 (25) | 682 (27) |
| 2010 | 1,997 (30) | 758 (30) |
| 2011 | 1,441 (22) | 527 (21) |
| Estimated glomerular filtration rate (ml/min/1.73 $m^2$) | | |
| 90+ | 2,022 (31) | 655 (26) |
| 60–89 | 3,965 (60) | 1,471 (59) |
| 45–59 | 525 (8) | 318 (13) |
| 30–44 | 81 (1) | 53 (2) |
| Diabetes mellitus | 1,173 (18) | 509 (20) |
| NSAIDs and/or high-dose aspirin | 34 (1) | 9 (0) |
| Type of therapy | | |
| Diuretic | 3,240 (49) | – |
| ACEI | 2,243 (34) | – |
| ARB | 1,110 (17) | – |
| Diuretic and ACEI | – | 1,663 (67) |
| Diuretic and ARB | – | 803 (32) |
| ACEI and ARB | – | 31 (1) |

*ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *NSAIDs* non-steroidal anti-inflammatory drugs

measurement within 365 days after the start of therapy. These were 1,687 and 545 for combined therapy, respectively. The associated cumulative probability of a renal function measurement was 18.8 % (95 % CI 17.9–20.0) at day 30 and 65.8 % (95 % CI 64.6–67.0) at day 365 after the start of single drug therapy (Fig. 1). For combined drug therapy, these were significantly higher, being 21.5 % (95 % CI 19.9–23.2) and 74.0 % (95 % CI 72.1–75.9), respectively. The univariable associations between baseline characteristics and the probability of a renal function measurement within 30 and 365 days after the index date are described in Table 2.

In the multivariable analyses, the probability of having one or more SCR measurements increased with calendar year, both for single drug therapy and combined therapy (Table 3). Also, baseline use of NSAIDs increased the probability of monitoring with both therapies, whereas age and eGFR was only associated with an increased probability of an SCR measurement following the start of single drug therapy. DM was significantly associated with the probability of an SCR measurement in a time-dependent manner; in the presence of DM, the probability of an SCR measurement increased with time from day 41 after the start of single therapy and day 40 after the start of dual therapy onwards. With single drug therapy, there was a significant interaction between DM and the type of therapy; in the absence of DM, the proportion of subjects with an SCR measurement was larger in the subgroup with ACEI-based single drug therapy as compared with subjects who started single drug therapy with a diuretic or an ARB. In contrast, there were no differences in monitoring within subjects with DM. No differences between types of therapy and monitoring were observed with combined drug therapy.

Between GP practices, there were significant differences in the cumulative probability of renal function monitoring, with a median probability of monitoring of 15.8 % (interquartile range [IQR] 7.0–27.8 %) at day 30 and a median of 62.5 % (IQR 50.0–74.9 %) at day 365 for single therapy, and 12.5 % (IQR 0.0–27.8 %) and 66.7 % (IQR 47.9–80.0 %) for combined drug therapy (Fig. 2).

In the cohort with single drug therapy, SCR increased by more than 30 % relative to baseline in 103 subjects (1.6 % of all subjects who started therapy). Review of the medical record revealed that in 29 subjects this might be caused by another medical condition, for example malignancy, cardiovascular events, or infection. Of the remaining 74 subjects, 32 received monotherapy, while 42 subjects were switched to combined drug therapy prior to the increase of SCR. In 59 (80 %) of the 74 subjects, this did not lead to subsequent SCR measurements within 1 month, a change of therapy, or referral to a specialist. In the cohort with combined drug therapy, SCR increased by >30 % relative to baseline in 85 subjects (3.4 % of all subjects who started therapy). In 16 subjects, other medical conditions might explain the increase. Of the remaining 69 subjects, 67 still used the same drug at the time of the increased SCR measurement. In 47 (70 %) of these 67 subjects, no actions were taken based on the results of the testing.

## 4 Discussion

This study shows three important issues. First, that in the majority (>75 %) of subjects renal function is not moni-

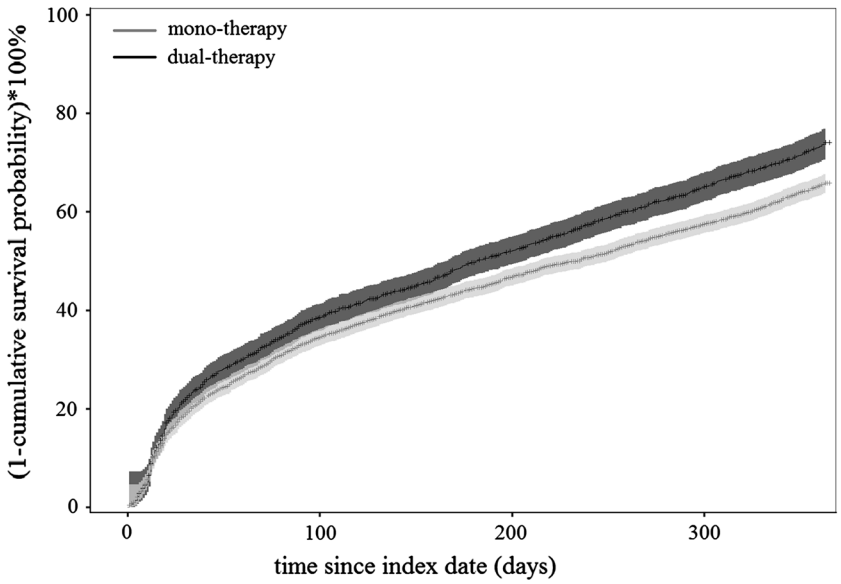


**Fig. 1** Renal function monitoring with single drug therapy and combined drug therapy

tored during the first 30 days after the start of (combined) antihypertensive therapy with diuretics and/or renin–angiotensin–aldosterone system inhibitors (RASIs) in contrast to recommendations of the guidelines. Second, there is large variability between GP practices with respect to renal function monitoring. Third, the incidence of renal impairment (increase in SCR measurement >30 % of baseline) during the first 365 days after treatment initiation is relatively low (2.6–3.4 %), and did not lead to subsequent actions in the majority (>70 %) of subjects.

Published data on the extent of monitoring during the first 30 days of antihypertensive therapy are limited. Findings in our study are consistent with the results from a previous study that had a far lower sample size [13]. No previous study has elaborated on differences between GP practices. Our findings suggest that this is relevant for further studies related to this topic. Our results suggest that monitoring might have improved modestly with calendar year, which was also observed in another study [12]. The extent of monitoring in subjects with DM in our study is much lower than what is reported in a study from Scotland where monitoring is assessed during approximately the same time window after the start of therapy [16]. Both in The Netherlands and the UK, periodic SCR measurement in subjects with DM is a quality indicator of healthcare. The discrepancy between both studies might thus be explained by differences in the respective performance management and payment system, which could be a subject for further study. Also, we found that DM increased the probability of monitoring, although not during the first 30 days. Possibly, renal function monitoring is performed in relation to DM rather than as part of antihypertensive therapy initiation. Unlike another study [16], we found an increased monitoring in subjects using NSAIDs and/or high-dose ASA at the time of index date, both with single drug therapy and when added to combination drug therapy, which has earlier been referred to as a 'triple whammy' [24]. However, this might also result from other factors associated with the use of NSAIDs, and the extent of monitoring is still low, particularly during the first 30 days (Table 2), despite the specific recommendation by the Dutch College of General Practitioners to monitor renal function if NSAIDs are used in combination with diuretics or RASIs [25]. This low rate is of concern as renal function might deteriorate within 2 days of NSAID initiation [26].

Subjects without DM who started single drug therapy with an ARB were monitored to the same extent as those starting therapy with a diuretic, but significantly less frequently than subjects initiating an ACEI, which is in line with results from other studies on monitoring [12, 16]. Still, this is surprising as results from the ONTARGET trial do not suggest a difference in renal impairment between ARBs and ACEIs [4]. The observed associations between calendar year and age, as well as the lack of a significant association for sex, are consistent with results of other studies [10, 12, 16].

The incidence of renal impairment (SCR measurement increased by >30 % relative to baseline measurement) within 365 days after index date in our study is higher than the rates of discontinuation of study medication due to renal impairment in the ONTARGET trial [4]. However, in the majority of patients in our study, the increase in SCR did not result in actions such as treatment discontinuation, specialist referral or subsequent SCR measurements. The controlled setting of a clinical study might explain the difference with monitoring in daily practice, as in our

**Table 2** Cumulative probability of a serum creatinine measurement within 30 and 365 days after the start of antihypertensive therapy

| | Single drug therapy | | | | Combined drug therapy | | | |
|---|---|---|---|---|---|---|---|---|
| | Day 30 | | Day 365 | | Day 30 | | Day 365 | |
| | Cum %[a] | 95 % CI | Cum %[a] | 95 % CI | Cum %[a] | 95 % CI | Cum %[a] | 95 % CI |
| Calendar year at start of treatment | | | | | | | | |
| 2005 | 8 | 3–23 | 50 | 35–67 | 25 | 7–69 | 88 | 58–99 |
| 2006 | 15 | 10–21 | 51 | 44–59 | 9 | 3–25 | 56 | 40–73 |
| 2007 | 13 | 10–17 | 59 | 55–64 | 17 | 11–25 | 73 | 64–81 |
| 2008 | 18 | 15–20 | 66 | 63–69 | 16 | 13–21 | 73 | 69–78 |
| 2009 | 17 | 15–19 | 65 | 63–67 | 20 | 17–23 | 74 | 70–77 |
| 2010 | 20 | 18–22 | 68 | 65–70 | 25 | 22–28 | 73 | 70–77 |
| 2011 | 23 | 21–25 | 71 | 65–76 | 26 | 23–30 | 90 | 70–99 |
| Age category (years) | | | | | | | | |
| 40–49 | 21 | 19–24 | 61 | 58–64 | 25 | 20–30 | 68 | 62–74 |
| 50–59 | 17 | 15–19 | 60 | 57–62 | 20 | 17–24 | 70 | 66–74 |
| 60–69 | 18 | 17–20 | 69 | 66–71 | 22 | 19–25 | 76 | 73–79 |
| 70–79 | 19 | 17–22 | 72 | 69–75 | 23 | 20–26 | 78 | 74–82 |
| 80+ | 22 | 18–26 | 76 | 71–81 | 20 | 15–26 | 76 | 69–81 |
| Sex | | | | | | | | |
| Male | 19 | 17–20 | 66 | 64–68 | 23 | 21–25 | 74 | 72–77 |
| Female | 19 | 18–20 | 66 | 64–68 | 21 | 19–23 | 74 | 71–76 |
| Estimated glomerular filtration rate (ml/min/1.73 $m^2$) | | | | | | | | |
| 90+ | 19 | 17–21 | 65 | 63–68 | 22 | 19–25 | 72 | 68–76 |
| 60–89 | 18 | 17–20 | 65 | 64–67 | 23 | 21–25 | 74 | 72–77 |
| 45–59 | 20 | 17–24 | 70 | 66–74 | 18 | 14–22 | 75 | 70–80 |
| 30–44 | 25 | 17–36 | 78 | 68–87 | 23 | 14–36 | 80 | 68–90 |
| Diabetes mellitus | | | | | | | | |
| No | 19 | 18–20 | 61 | 60–62 | 23 | 21–25 | 69 | 67–71 |
| Yes | 19 | 17–22 | 87 | 84–89 | 18 | 15–21 | 92 | 89–94 |
| Concomitant use of NSAIDs and/or high-dose aspirin | | | | | | | | |
| No | 19 | 18–20 | 66 | 64–67 | 22 | 20–24 | 74 | 72–76 |
| Yes | 18 | 8–35 | 83 | 69–94 | 11 | 2–57 | 85 | 53–99 |
| Type of therapy | | | | | | | | |
| Diuretic | 17 | 16–18 | 64 | 62–66 | – | – | – | – |
| ACEI | 24 | 23–26 | 73 | 71–75 | – | – | – | – |
| ARB | 14 | 12–16 | 57 | 54–60 | – | – | – | – |
| Diuretic and ACEI | – | – | – | – | 25 | 23–28 | 75 | 73–78 |
| Diuretic and ARB | – | – | – | – | 15 | 12–17 | 71 | 68–74 |
| ACEI and ARB | – | – | – | – | 19 | 9–38 | 79 | 63–92 |

*ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] Cumulative percentage (1 − cumulative survival probability) × 100 %

study. It is important to note that the rate of AKI might be even higher in subjects with additional risks factors, such as heart failure and moderate–severe CKD, who were not included in our study population. As with monitoring of renal function after the start of antihypertensive therapy in general (Fig. 2), recognition of accelerated decline of renal function and AKI from antihypertensive therapy might also differ between GPs; however, the low numbers precluded further analysis.

The strengths of our study include its population-based design as well as the stringent criteria applied to minimize the risk of underestimation of renal function monitoring. Indeed, we excluded short-term therapy or patients who switched therapy, as well as patients likely to be monitored

**Table 3** Multivariable analysis: renal function monitoring after the start of antihypertensive therapy

| Characteristic | Single drug therapy[d] | | | | Combined drug therapy[d] | | | |
|---|---|---|---|---|---|---|---|---|
| | Est | HR | *p*-value | 95 % CI | Est | HR | *p*-value | 95 % CI |
| Calendar year at start of treatment (2011 = ref.) | | | | | | | | |
| 2005 | −0.88 | 0.42 | **0.001** | 0.25–0.69 | 0.21 | 1.23 | 0.695 | 0.43–3.53 |
| 2006 | −0.37 | 0.69 | **0.005** | 0.53–0.89 | −0.26 | 0.77 | 0.345 | 0.45–1.32 |
| 2007 | −0.51 | 0.60 | **<0.001** | 0.51–0.72 | −0.25 | 0.78 | 0.106 | 0.58–1.05 |
| 2008 | −0.34 | 0.71 | **<0.001** | 0.62–0.81 | −0.33 | 0.72 | **0.001** | 0.59–0.88 |
| 2009 | −0.29 | 0.75 | **<0.001** | 0.67–0.84 | −0.23 | 0.79 | **0.008** | 0.67–0.94 |
| 2010 | −0.15 | 0.86 | **0.006** | 0.78–0.96 | −0.07 | 0.93 | 0.414 | 0.79–1.1 |
| Age category, years (40–49 = ref.) | | | | | | | | |
| 50–59 | −0.09 | 0.92 | 0.116 | 0.83–1.02 | −0.08 | 0.93 | 0.434 | 0.76–1.12 |
| 60–69 | 0.08 | 1.08 | 0.129 | 0.98–1.21 | 0.08 | 1.09 | 0.396 | 0.9–1.31 |
| 70–79 | 0.08 | 1.08 | 0.215 | 0.96–1.22 | 0.11 | 1.12 | 0.289 | 0.91–1.38 |
| 80+ | 0.21 | 1.24 | **0.011** | 1.05–1.46 | 0.12 | 1.12 | 0.383 | 0.86–1.46 |
| Sex (male = ref.) | | | | | | | | |
| Female | 0.01 | 1.01 | 0.853 | 0.94–1.08 | 0.04 | 1.04 | 0.469 | 0.94–1.16 |
| Estimated glomerular filtration rate, ml/min/1.73 $m^2$ (90+ = ref.) | | | | | | | | |
| 60–89 | 0.06 | 1.06 | 0.167 | 0.98–1.15 | −0.04 | 0.96 | 0.601 | 0.84–1.1 |
| 45–59 | 0.17 | 1.19 | **0.018** | 1.03–1.37 | −0.01 | 0.99 | 0.933 | 0.81–1.22 |
| 30–44 | 0.19 | 1.21 | 0.194 | 0.91–1.62 | 0.32 | 1.38 | 0.098 | 0.94–2.03 |
| Concomitant use of NSAIDs and/or high-dose aspirin (no use = ref.) | | | | | | | | |
| Yes | 0.45 | 1.58 | **0.027** | 1.05–2.36 | 0.86 | 2.35 | **0.028** | 1.1–5.05 |
| Type of therapy[a,b] (type 1 = ref.) | | | | | | | | |
| Type 2 | 0.28 | | **<0.001** | – | −0.03 | 0.97 | 0.626 | 0.85–1.1 |
| Type 3 | −0.11 | | 0.082 | – | 0.07 | 1.08 | 0.756 | 0.67–1.72 |
| Diabetes mellitus (absent = ref.) | | | | | | | | |
| Present | 0.15 | | 0.086 | – | −0.25 | | **0.016** | – |
| Diabetes mellitus × time interaction[c] | | | | | | | | |
| Diabetes mellitus × type of therapy interaction[a,b] | 0.16 | | **<0.001** | – | 0.23 | | **<0.001** | – |
| Diabetes mellitus present and type 2 therapy | −0.25 | | **0.005** | – | – | – | – | – |
| Diabetes mellitus present and type 3 therapy | 0.11 | | 0.378 | – | – | – | – | – |

Bold values indicate statistical significance at $p < 0.05$

*ACE* angiotensin-converting enzyme, *ACEI* ACE inhibitor, *ARB* angiotensin receptor blocker, *Est* estimate, *HR* hazard ratio, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] Hazard rates and 95 % CI intervals are not provided for characteristics included in an interaction term

[b] Type of therapy: single drug: type 1, diuretic; type 2, ACEI; type 3, ARB; combined drug: type 1, diuretic and ACE; type 2, diuretic and ARB; type 3, ACEI and ARB

[c] If diabetes mellitus is present, the estimate for the diabetes mellitus time interaction should be multiplied with the natural logarithm of the number of days after day 41 following the start of single drug therapy or the number of days after day 40 following the start of combined drug therapy

[d] Fully adjusted model

by the specialist, although this inevitably limits the generalizability of our results to subjects without additional risks factors for AKI. In addition, despite these aforementioned criteria, a small number of subjects might have received specialist care following a referral that was not preceded by an SCR measurement by the GP.

The incidence of non-dialysis requiring community-based AKI has strongly increased between 1996 and 2003 [27], despite renoprotection with ACEI and/or ARBs, and it has been argued that the use of these medications might underlie this trend [28]. This applies at least to subjects on dual RAAS blockade [29, 30] which is currently evaluated during an article 31 referral procedure by the European Medicines Agency (EMEA/HA/31/1370). Another study showed that several barriers might impede monitoring [31]. Comparison of our findings with the results of Kalra and

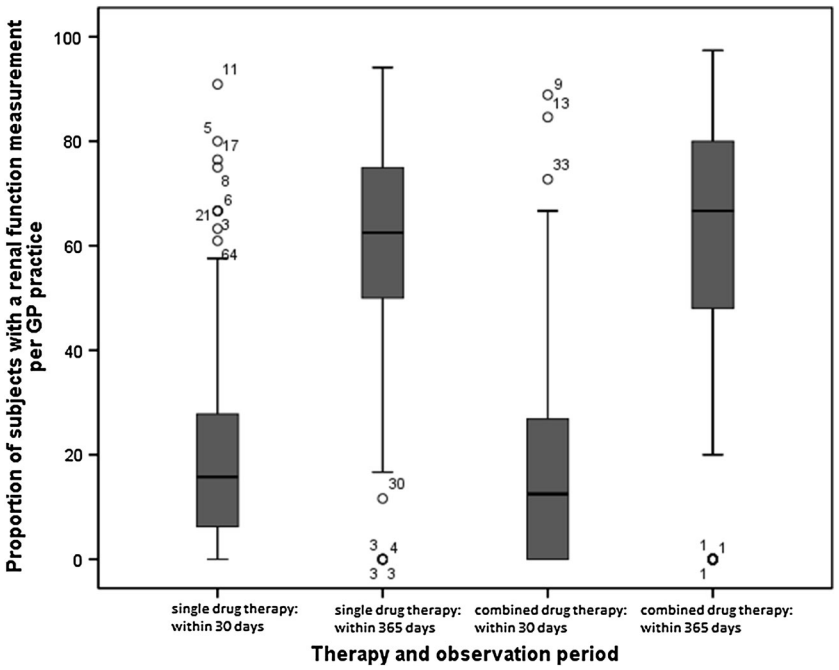


**Fig. 2** Renal function monitoring with single drug therapy and combined drug therapy across GP practices. *GP* general practitioner, *horizontal bar* median, *boxes* interquartile range, *t-bars* 1.5-extension of the 2nd and 3rd quartile, *numbers* subjects per practice that started single drug therapy and combined drug therapy respectively for outlying observations, *proportion* (1-cumulative survival probability) × 100 %

colleagues [8] suggest that the success of initiatives to bring down these barriers is limited thus far. An obvious reason for a failure to embrace monitoring enthusiastically is the very low yield on screening, at least in our study population, in which SCR increased by >30 % from baseline in just 1.6–3.4 % of subjects, whereas in a previous large ($n = 74{,}096$) study, hyponatremia, hyperkalemia and hypokalemia were only observed in 0.7, 0.8 and 1.3 % of subjects within 6 months of the initiation of antihypertensive treatment [17].

Studies, including randomized clinical trials, report that quality indicators improve with the use of financial incentives to directly reward performance and 'quality' in healthcare [32, 33]. There are no established indicators for renal function monitoring due to inter-individual differences in renal function decline with ageing and underlying disease, as well as the absence of validated markers of renal renin–angiotensin system activity to identify subjects who are at increased risk of renal impairment or AKI [34, 35].

## 5 Conclusions

Our study shows that the extent of renal function monitoring with antihypertensive therapy might be substantially improved. Renal impairment was found to complicate antihypertensive therapy. In a majority of cases, other medical conditions that might explain the renal impairment were lacking. Subsequent actions were not taken in the majority (>70 %) of subjects. Future studies should examine to what extent an increase in SCR >30 % of baseline is associated with patient harm. Also, the implementation of quality indicators to monitor antihypertensive therapy during the first year after the start of, or change in, antihypertensive therapy should be investigated, including their impact on the individual practice, as our study shows a large variability in the extent of monitoring between practices.

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