Prescription Rates of Cardiovascular Medications in a Large UK Primary Care Chronic Kidney Disease Cohort

Rupert Major, David Shepherd, Graham Warwick, Nigel Brunskill

Department of Nephrology, Leicester General Hospital, and Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

Background and Aims: Chronic kidney disease (CKD) is associated with increased cardiovascular (CV) risk. Guidelines have suggested the universal use of statins in CKD but aspirin's role is less well defined. The aim of this study was to determine prescription rates for statins and aspirin in a UK-based CKD cohort and to establish factors that influenced prescription rates.

Methods: We used data from a UK primary care CKD cohort to study rates of prescription of statins and aspirin. Simple rates were initially calculated. Binary logistic regression was utilized with either statin or aspirin prescription as the outcome variable and covariates including demographic details and comorbidities.

Results: There were 31,056 individuals in the cohort with at least one estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m², and 65.1% individuals had 2 eGFR results <60 ml/min/1.73 m² more than 3 months apart. Mean eGFR at baseline was 51.1 ml/min/1.73 m² (SD 9.1), and 64.9% had a diagnosis of hypertension (HTN), 18.8% had diabetes mellitus (DM) and 29.8% a history of CV disease. Statins were prescribed to 14,972 (48.2%) and aspirin to 11,023 (35.5%). The regression model suggested that CV disease, HTN and DM influenced the prescription of statins and aspirin but overall CKD stage, calculated by either eGFR or proteinuria, did not.

Conclusions: Prescriptions of statins and aspirin in CKD is based more on the presence of comorbidities than the CKD severity. Further physician and patient education of the increased CV risk associated with CKD and its suitability for CV medication intervention is required.
the risk of bleeding events [5]. Furthermore, lipid profile abnormalities become increasingly disparate as CKD advances in severity [6] and surrogate measurements such as low density lipoprotein reduction may be more difficult to interpret in CKD. Most clinical trials exclude patients with ‘severe’ CKD [7], commonly defined as an estimated glomerular filtration rate (eGFR) or creatinine clearance of <60 ml/min/1.73 m². This limits the applicability of the evidence to many CKD patients. Furthermore, nephrology may be the most under-represented medical sub-speciality in clinical trials [7]. Consequently, the ability of primary and secondary care physicians to make evidence-based decisions regarding primary and secondary CV risk prevention in CKD patients is restricted. Recently, National Institute for Health and Care Excellence [8] and Kidney Disease Improving Global Outcomes (KDIGO) [9] guidelines have recommended the use of statins for all individuals with CKD. However, there remains limited evidence for the use of aspirin, particularly for primary prevention in CKD.

Given these uncertainties it is possible that opportunities to manage CV risk factors in primary care may be passed over. Using a large database of CKD patients identified in primary care, this study aimed to establish the prescription rates of the commonly used CV medications, statins and aspirin. The use of these medications alongside common CV related comorbidities was also assessed.

Methods

We analyzed the baseline cross-sectional data from ‘The Primary-Secondary Care Partnership to Prevent Adverse Outcomes in Chronic Kidney Disease’ (PSP-CKD) study (ClinicalTrials.gov identifier: NCT01688141). PSP-CKD is a cluster randomized controlled trial of CKD management in primary care. The study is approved by the local Research Ethics Committee. The intervention is a nurse practitioner-led CKD management programme in primary care with secondary care nephrology support versus usual primary care management, essentially general practitioner led management of CKD. Randomization is at the level of the general practice and individual patient consent was not sought. In total, 49 practices were recruited from Northamptonshire, UK, and completed participation in the trial. The trial commenced in 2010 with the extraction of baseline data before practices were randomly allocated to either the intervention or control groups. This paper reports the study’s baseline data.

A web-based CKD management and audit software tool, Improving Patient Care and Awareness of Kidney Disease Progression Together (IMPAKT) [10], was developed to identify all CKD patients in participating practices from practice electronic medical records. For eGFR data, IMPAKT used Morbidity Information Query and Export Syntax (MIQUEST) search methodology to analyze the practice record of all adult patients retrospectively back to 2005 for any eGFR <60 ml/min/1.73 m²and, where more than one eGFR value <60 ml/min/1.73 m²was available, calculated the time interval between results. Individuals either receiving maintenance dialysis or with a renal transplant were excluded. For other biomedical data related to these patients, IMPAKT extracted data most temporally close to the practice randomization date. For medications, IMPAKT extracted the relevant information if it had been prescribed within 6 months of the extraction date.

For the purposes of the study, an anonymized data set from each practice was exported to University of Leicester Clinical Trials Unit to assemble a prospective CKD database from all participating practices. The data comprises anthropometric, demographic, relevant medical history, prescribed medications, blood and urine test results.

The eGFRs were reported using the MDRD equation [11]. Proteinuria data were derived from 2 sources, urine dipstick results and urine protein quantification by either albumin creatinine ratio (ACR) or protein creatinine ratio (PCR). Where both ACR and PCR were available, the latter was used for classification due to its better calibration to the gold standard, 24-hour urine protein measurement [12]. Individuals were assigned to a CKD stage based on KDIGO guidelines for both eGFR and proteinuria [13]. CV disease includes any individual with a Read code diagnosis of previous ischemic heart disease, stable angina, cerebrovascular accident, transient ischemic attack or heart failure. Read codes are nationally standardized medical codes used in UK primary care (online suppl. material, see www.karger.com/doi/10.1159/000445387).

Data are reported for continuous outcomes as mean ± SD and for categorical variables as counts and percentage. Statin and aspirin prescriptions were the outcomes of interest. Simple unadjusted prescription rates were calculated. Binary logistic regression was performed using the prescription of either statins or aspirin as the outcome variables. The regression models were calculated across the whole cohort and also for individuals without any pre-existing CV disease, the primary prevention cohort. Gender, age, CKD stage based on eGFR and proteinuria quantification and comorbidities were used as covariates. Confirmed CKD, the ‘CKD cohort’, refers to individuals who had at least 2 eGFRs <60 ml/min/1.73 m² measured at least 3 months apart [13].

Initially eGFR and age were considered as categorical variables, CKD stage and age group by decade, and then as continuous variables, eGFR in ml/min/1.73 m² and age in years. Other variables remained unchanged. For proteinuria stage, CKD stage and age group categorical covariates, stage A1, stage 3A and <50 years respectively were used as the reference groups. All statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM), with p < 0.05 taken to reflect statistical significance.

Results

The records of 353,256 registered patients ≥18 years of age from 49 practices were analyzed. The baseline cohort data of the PSP-CKD study included 31,056 (8.8%) individuals with at least 1 eGFR <60 ml/min/1.73 m², referred to henceforth as the ‘eGFR cohort’. Of the eGFR cohort,
65.1% of patients (20,276 individuals) had 2 or more eGFR results <60 ml/min/1.73 m² >3 months apart and are henceforth referred to as the ‘CKD cohort’. The CKD cohort has ‘true’ CKD as defined by KDIGO and represent 5.7% of the total practice population ≥ 18 years of age. In the eGFR cohort, 9,291 (29.9%) individuals had a coded history of CV disease. Table 1 shows the full baseline descriptors of the eGFR cohort.

The eGFR cohort had a mean eGFR at baseline of 51.1 ml/min/1.73 m² (SD 9.1) and 80.9% had CKD stage 3A. Table 2 shows the frequency and percentage of overall CKD stage based on eGFR and proteinuria, including information on missing proteinuria data, in the eGFR cohort; 20,169 (64.9%) had a coded diagnosis of hypertension (HTN) and 5,819 (18.8%) a coded diagnosis of DM. Mean systolic blood pressure was 133.8 mm Hg (SD 16.3) and mean diastolic blood pressure 75.4 mm Hg (SD 10.0). Altogether 3,230 (10.4%) of the eGFR cohort were current smokers and 11,353 (36.6%) ex-smokers.

In the eGFR cohort, 14,972 (48.2%) were prescribed statins and 11,023 (35.5%) individuals aspirin, and 73.2% of individuals with known CV disease were prescribed a statin compared to 37.6% without known CV disease (Pearson χ² < 0.001, OR 4.53, 95% CI 4.30–4.78). A similar relationship occurred for aspirin (Pearson χ² < 0.001, OR 7.46, 95% CI 7.07–7.88). Higher rates of prescriptions for both medication groups were found for patients with HTN, DM or with ≥2 recorded eGFRs (χ² < 0.001 for all) compared to those without the condition. Statin prescription rates varied signifi-
cantly across age groups, peaking in the 70–79 years group (58.7%), whilst decreasing as age both increased and decreased. Figure 2 shows statin and aspirin prescription rates by age groups. Rates of statin prescription increased in the eGFR cohort as CKD stage worsened. There was a statistically significant trend when CKD stage was used as a categorical variable (p < 0.01 for linear-by-linear association). When eGFR was used as a continuous variable, a similar correlation was found (β co-efficient –0.016, p < 0.001). Mean total cholesterol was lower in the statin group (4.5 mmol/l, mean difference 0.88 mmol/l, p < 0.001, 95% CI 0.85–0.91).

Binary logistic regression was performed for statin and aspirin prescription (table 3). For binomial covariates, all tested variables (CV disease, HTN, DM, confirmed CKD and male gender) were all associated with statins and aspirin prescriptions (p value ≤0.001 for all). Age groupings in the regression model showed a similar pattern to percentage of prescription in the initial comparison. The peak group was again the 70–79 age bracket (OR 3.20, p < 0.001 for both medication groups), with a similar decrease in the OR as the ages increased and decreased. When eGFR was treated as a continuous variable, a 1 ml/min/1.73 m² change in eGFR was not significantly associated with statin prescription (β co-efficient –0.003, p = 0.09) but was associated with aspirin prescription (β co-efficient –0.011, p < 0.001).

Table 2. Frequencies and percentage of whole PSP-CKD study eGFR cohort by GFR and proteinuria stage

| Proteinuria stage | A1     | A2     | A3     | no data | total   |
|-------------------|--------|--------|--------|---------|---------|
| eGFR stage        |        |        |        |         |         |
| 3A                | 14,029 (45) | 1,832 (6) | 1,717 (6) | 7,549 (24) | 25,127 (81) |
| 3B                | 2,115 (7)  | 570 (2)  | 469 (2)  | 1,101 (4)  | 4,255 (14)  |
| 4                 | 352 (1)   | 148 (1)  | 220 (1)  | 254 (1)   | 974 (3)     |
| 5                 | 47 (<1)   | 31 (<1)  | 77 (<1)  | 87 (<1)   | 242 (1)     |
| No eGFR data      | 134 (<1)  | 15 (<1)  | 36 (<1)  | 273 (1)   | 458 (2)     |
| Total             | 16,677 (54) | 2,596 (8) | 2,519 (8) | 9,264 (30) | 31,056     |

Fig. 1. Rates of statin and aspirin prescriptions by presence of comorbidities in eGFR cohort.
**Table 3.** ORs and p values with 95% CIs of multivariate logistic regression model for eGFR cohort

|                      | Statin                        | Aspirin                       |
|----------------------|-------------------------------|-------------------------------|
|                      | OR (95% CI)                   | p value                       | OR (95% CI)                   | p value                       |
| Known CV disease     |                               |                               |                               |                               |
| HTN                  | 4.64 (4.37–4.93)              | <0.01                         | 6.04 (5.70–6.39)              | <0.01                         |
| DM                   | 2.01 (1.90–2.12)              | <0.01                         | 1.48 (1.40–1.57)              | <0.01                         |
| ≥2 eGFRs <60         | 3.21 (2.99–3.44)              | <0.01                         | 1.56 (1.46–1.67)              | <0.01                         |
| Male                 | 1.44 (1.36–1.53)              | <0.01                         | 1.29 (1.21–1.37)              | <0.01                         |
| Age group (<50 years reference), years |                               |                               |                               |                               |
| 50–59                | 1.94 (1.65–2.30)              | <0.01                         | 1.45 (1.18–1.80)              | <0.01                         |
| 60–69                | 2.93 (2.52–3.42)              | <0.01                         | 2.45 (2.02–2.97)              | <0.01                         |
| 70–79                | 3.20 (2.75–3.73)              | <0.01                         | 3.20 (2.65–3.86)              | <0.01                         |
| 80–89                | 1.89 (1.62–2.20)              | <0.01                         | 3.29 (2.72–3.97)              | <0.01                         |
| 90+                  | 0.72 (0.60–0.86)              | <0.01                         | 3.30 (2.68–4.06)              | <0.01                         |
| Proteinuria stage (A1 reference) |                             |                               |                               |                               |
| A2                   | 0.97 (0.88–1.06)              | 0.48                          | 1.02 (0.93–1.13)              | 0.64                          |
| A3                   | 0.96 (0.88–1.06)              | 0.46                          | 1.03 (0.93–1.13)              | 0.62                          |
| eGFR stage (3A reference) |                               |                               |                               |                               |
| 3B                   | 0.97 (0.90–1.05)              | 0.47                          | 1.10 (1.02–1.19)              | 0.01                          |
| 4                    | 1.16 (1.00–1.35)              | 0.05                          | 1.37 (1.18–1.59)              | <0.01                         |
| 5                    | 1.70 (1.27–2.29)              | <0.01                         | 2.48 (1.85–3.33)              | <0.01                         |

Outcome variable – statin or aspirin prescription. All covariates and reference groups for the model are shown.

*Fig. 2.* Rates of statin and aspirin prescriptions by age groups.
Discussion

The PSP-CKD study of patients with eGFRs <60 ml/min/1.73 m² was derived from a large number of general practices in Northamptonshire and is likely to be broadly typical of UK primary care CKD patients.

The results of the current study suggest that both statins and aspirin are widely used in CKD. Furthermore, the use of both medications is significantly increased in association with DM, HTN and established CV disease in CKD patients. All these comorbidities are positively associated with future CV events, with CV disease and CKD the most influential [3]. However, the regression analysis suggests that severity of CKD has, at best, a minor influence on rates of prescriptions for these medications even though CV risk increases as CKD progresses [13]. Only stage 5 CKD showed significantly higher rates of prescriptions in the regression models. This may be linked to these patients being more likely to be managed in secondary care.

Overall, the prescription rates for both statins and aspirin in this cohort of CKD patients, particularly in those with DM or pre-existing CV disease, are lower than would be expected if relevant guidelines were fully implemented [8, 9, 13–15]. This finding is in agreement with previous studies describing disappointing levels of primary care prescribing in DM and for primary and secondary prevention of CV disease [16–20]. In England, the Quality and Outcomes Framework rewards primary care for the appropriate use of statins and aspirin in relevant conditions, and providing such financial incentives has been shown to be effective in the management of DM [21]. The current analysis indicates room for substantial improvement in prescribing for management of CV risk in CKD. Established CVD, DM and HTN are all well-established factors that influence aspirin and statin prescriptions for the purpose of reducing CVD events [16, 20]. The low prescription rates for statins and aspirin in uncomplicated CKD, compared to CKD associated with DM, CV disease and/or hypertension in the current study suggests that CKD is not widely regarded as a key risk factor for CV disease in its own right. This is further highlighted by the absent association of worsening CKD with statin and aspirin prescriptions.

The use of statins to lower CV morbidity and mortality in CKD is well established [22–25]. The role of aspirin in CKD is less clear. Evidence for its use in CKD is limited and appears to show limited benefit with possible increased risk of bleeding [26]. Observational data also suggests that aspirin may increase CV risk and bleeding risk [27]. Therefore whilst higher levels of CV disease may make universal use of aspirin in CKD an attractive proposition an increased risk of bleeding may negate any benefit.

The PSP-CKD cohort identified using IMPAKT has similar characteristics to that previously described in the New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) study [1]. Both studies utilize similar methodology to identify CKD and associated comorbidities from primary care electronic records. Comorbidities are similar in both cohorts with hypertension being present in approximately two-thirds of individuals and DM in around 20% in PSP-CKD and 14% in NEOERICA. Both cohorts consisted of approximately 60% females and had a similar mean age in the low seventies.

However, unlike NEOERICA, the PSP-CKD study was able to identify individuals where the diagnosis of CKD was confirmed by at least 2 eGFRs <60 ml/min/1.73 m² more than 3 months apart. In PSP-CKD all adults with a single eGFR <60 ml/min/1.73 m² were identified, and of these nearly two thirds had at least one additional eGFR of <60 ml/min/1.73 m² in an appropriate time period. The use of a single eGFR to diagnose and classify CKD will tend to overestimate prevalence. Differences in methodology therefore explain the reported true CKD prevalence of 5.7% in PSP-CKD compared to 8.5% in NEOERICA. Interestingly, based on a single eGFR <60 ml/min/1.73 m², the prevalence of CKD in PSP-CKD is 8.9% and very similar to NEOERICA. The current data indicate that around 30% of primary care patients with a single low eGFR require repeat testing. One of the key drivers underlying the various CKD clinical guidelines is to mitigate the CV risk associated with CKD. Therefore, it is of considerable importance to assess whether opportunities to intervene with risk modification strategies are fully exploited.

The use of IMPAKT has facilitated the accumulation of a rich database of primary care CKD patients. However, this analysis has a number of limitations. The participating general practices, although large in number, were not randomly selected and thus may not be fully representative of the UK population. Furthermore, the primary purpose of this work was not to study medication prescription rates and therefore it is subject to similar limitations and risk of bias common to post-hoc analyses. Also, observational data may not account for other confounding factors that may have influenced the prescription rates of these medications. Prescription data
within electronic records does not equate to medication dispensing or adherence by the patient. The data set also had no internal audit function to verify the accuracy of coding of medical conditions within the electronic records. This is most likely to underestimate the prevalence of comorbidities if conditions have not been correctly coded in individual records. Approximately a third of our cohort did not have a second, and confirmatory, eGFR <60 ml/min/1.73 m². Whilst initial univariate analysis suggested that not confirming the diagnosis of CKD with a follow-up eGFR might influence the decision to prescribe either medications, this effect was reduced in the multivariate analysis. This suggests that individuals with comorbidities such as DM or pre-existing CVD were more likely to have confirmatory eGFR checked.

Overall, the current data suggest that statin and aspirin use in CKD is based more on the presence of comorbidities, and particularly the presence of CV disease, than CKD severity, based on either eGFR or proteinuria. Further education of the increased CV risk associated with CKD and its suitability for CV medication intervention may increase prescription rates and improve CV outcomes in CKD.

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### Disclosure Statement

The authors have no conflicts of interest to declare.

### Statement of Ethics

The PSP study was approved by the local research ethics committee.

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