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SHORT COMMUNICATION

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Statin use before and after the KDIGO Lipids in chronic kidney disease guideline: A population-based interrupted time series analysis

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Abstract

In November 2013, the *Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* was published, recommending statins for all individuals 50 years or older with an estimated glomerular filtration rate below 60 ml/min/1.73 m^2 to lower the risk of major cardiovascular events. We quantified the prevalence of statin use among the target population before and after the guideline publication in a large Danish cohort of individuals with an estimated glomerular filtration rate below 60 ml/min/1.73 m^2, to investigate the effect of the guideline, but found no difference in the prevalence of statin use prior to and after the guideline publication.

KEYWORDS
chronic kidney disease, guidelines, statins

1 | INTRODUCTION

Patients with chronic kidney disease (CKD) are at increased risk of major cardiovascular events.[1] Multiple randomized, controlled trials have reported statins to reduce this risk by up to 17%.[2–4] Since 2013, the *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* has recommended statin and/or ezetimibe treatment to all who are 50 years or older, with an estimated Glomerular Filtration Rate (eGFR) below 60 ml/min/1.73 m^2, except for individuals receiving dialysis treatment.[5] There is little evidence on the adherence to the 2013 KDIGO Guidelines for lipid management.[6,7]

Therefore, we aimed to estimate the impact of the KDIGO guideline publication on the clinical implementation of statin treatment in an unselected population of patients with an eGFR below 60 ml/min/1.73 m^2.

2 | MATERIALS AND METHODS

Using a population-based laboratory cohort, we performed a controlled interrupted time series analysis quantifying the prevalence of statin use prior to and after the publication of the 2013 KDIGO Lipids in CKD guidelines among all individuals who were 50 years or older, with an estimated eGFR below and above 60 ml/min/1.73 m^2 on the island of Funen, Denmark.

2.1 | Study population

Data on more than 450,000 Danish residents were obtained from the Funen Laboratory Cohort, which holds complete information on creatinine measurements, prescription drug use and hospital diagnoses for all residents on the island of Funen, Denmark, during the study period of 15 February 2011 to 21 October 2015.[8] The study period was divided into 90-day intervals before ($N = 11$) and after 1 November 2013 ($N = 8$). On the first day of every interval, we identified all individuals aged 50 years or older with at least two creatinine measurements during the previous year. Individuals were classified according to the median eGFR measured during the previous year (below or above 60 ml/min/1.73 m^2), and individuals who had previously received hemo- or peritoneal dialysis were excluded.

2.2 | Exposure

The exposure of interest was the introduction of the KDIGO Lipids in CKD guideline ('the intervention'), which was introduced in November 2013. The guideline was implemented in the Danish guidelines by the Danish Nephrology Society the same year.[9] Individuals in all 90-day intervals prior to November 2013 were classified as unexposed, while all later intervals were considered exposed.

2.3 | Outcome

The outcome of interest was the period prevalence of statin use for each 90-day interval. Statin use was defined as any prescription fill for a statin. Any individual who filled a prescription for statins during the 3 months following the index date was considered a statin user.

2.4 | Statistical analyses

We fitted a segmented regression model (shown in the supporting information)[10] to obtain the yearly trend and the immediate difference in the proportion of statin users before and after the guideline publication among individuals with an eGFR above and below 60 ml/min/1.73 m^2. Further, we calculated the difference in the proportion of statin users 1 year after the guideline publication between the observed scenario, and a counterfactual scenario where the guideline was not implemented (counterfactual difference), and the estimated pre-intervention trend was assumed to continue throughout the study period.

In supplementary analyses, we obtained estimates stratified by kidney function (eGFR 30–59, 15–29, <15 ml/min/1.73 m^2), age (50–69 and 70+), sex and indication of statin use. Individuals without a history of acute myocardial infarction, ischaemic stroke or peripheral vascular disease were assumed to receive primary prophylaxis, while individuals with a history of above-mentioned diagnoses were considered to receive secondary prophylaxis. Finally, we also calculated the 180-day period prevalence of statin use at the beginning and end of the study period.

Codes used to define prescription drugs, diagnoses and conditions are shown in Table S1.

3 | RESULTS

Overall, we included 19,743 individuals with a median eGFR < 60 ml/min/1.73 m^2 who were 50 years or older and not on dialysis across all evaluated periods. The number of patients included during the first 90-day interval of the study period was 6765 and gradually increased to 10,194 included individuals during the last interval. At the time of the guideline publication, the median age was 79 years and 52% were females. When stratifying on the estimated kidney function, 84% were classified as CKD stage 3 (eGFR 30–59 ml/min/1.73 m^2); 14% CKD stage 4 (eGFR 15–29 ml/min/1.73 m^2) and 2.1% CKD stage 5 (eGFR < 15 ml/min/1.73 m^2 not on dialysis) (Table S2).

The overall period prevalence of statin use was 39% at the start and end of the inclusion period. No difference between the pre- and post-KDIGO guideline publication was observed when comparing the yearly pre-intervention trend (+0.1%, 95% confidence interval −0.5% to 0.7%) and post-intervention trend

TABLE 1 Differences in the prevalence proportion of statin use stratified on kidney function, indication for statin use, age and sex

Group	Immediate difference (%)	Counterfactual difference (%)	Pre-intervention trend (%/year)	Post-intervention trend (%/year)
Any prescription redemption				
eGFR <60 ml/min/1.73 m^2	−0.1 (−1.1 to 1.0)	−0.1 (−1.3 to 1.2)	0.1 (−0.5 to 0.7)	0.1 (−0.6 to 0.8)
eGFR 60+ ml/min/1.73 m^2	0.7 (0.3 to 1.1)	0.8 (0.4 to 1.3)	−0.5 (−0.7 to −0.3)	−0.4 (−0.6 to −0.1)
CKD stage				
CKD3	0.1 (−1.0 to 1.2)	−0.0 (−1.4 to 1.4)	0.1 (−0.5 to 0.7)	−0.0 (−0.8 to 0.7)
CKD4	−1.4 (−4.3 to 1.5)	−0.5 (−4.1 to 3.1)	−0.3 (−1.9 to 1.3)	0.6 (−1.3 to 2.6)
CKD5	1.1 (−6.8 to 9.0)	1.0 (−8.4 to 10.3)	1.3 (−2.7 to 5.3)	1.2 (−4.2 to 6.6)
Indication				
Primary prophylaxis	0.5 (−0.7 to 1.7)	0.6 (−0.9 to 2.1)	0.3 (−0.3 to 1.0)	0.4 (−0.4 to 1.2)
Secondary prophylaxis	−0.3 (−2.1 to 1.5)	−0.8 (−3.0 to 1.4)	0.0 (−1.0 to 1.0)	−0.5 (−1.7 to 0.8)
Sex				
Female	0.4 (−1.1 to 1.8)	0.2 (−1.5 to 2.0)	0.1 (−0.7 to 0.9)	−0.0 (−1.0 to 0.9)
Male	−0.4 (−1.9 to 1.1)	−0.4 (−2.2 to 1.5)	0.1 (−0.8 to 0.9)	0.1 (−0.8 to 1.1)
Age				
50–69	−0.2 (−2.7 to 2.2)	−0.8 (−3.7 to 2.2)	−0.3 (−1.6 to 1.0)	−0.9 (−2.5 to 0.7)
70+	0.0 (−1.1 to 1.1)	0.1 (−1.3 to 1.6)	0.2 (−0.4 to 0.9)	0.4 (−0.4 to 1.1)
New use				
eGFR <60 ml/min/1.73 m^2	0.1 (−0.3 to 0.6)	0.1 (−0.4 to 0.5)	0.0 (−0.2 to 0.2)	−0.0 (−0.3 to 0.2)
eGFR 60+ ml/min/1.73 m^2	0.1 (−0.0 to 0.3)	0.1 (−0.1 to 0.3)	−0.0 (−0.1 to 0.0)	−0.1 (−0.2 to 0.0)

Note: The immediate difference is the estimated difference in the prevalence proportion immediately before and after the publication of the KDIGO guideline. The counterfactual difference is the estimated difference in the prevalence proportion 1 year after the publication of the *Kidney Disease: Improving Global Outcomes* (KDIGO) guideline, compared to the estimated prevalence proportion the pre-intervention trend has continued throughout the study period.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

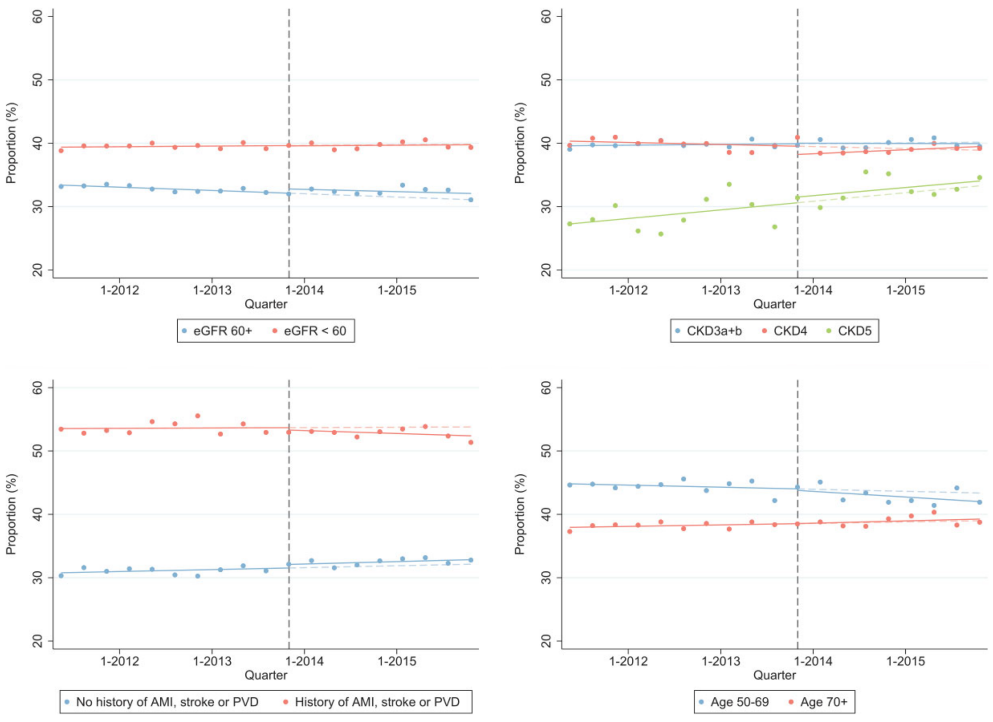

FIGURE 1 The 90-day period prevalence of statin use during the study period.

(+0.1% per year, −0.6% to 0.8%) (shown in Table 1 and Figure 1). In the control series, consisting of individuals with a median eGFR ≥60 ml/min/1.73 m^2, we found no difference in the period prevalence at the start (14,046/42,345, 33%) and end (20,654/66,465, 31%) of the study period (Table S3). Likewise, no difference in trend prior to (−0.5% per year −0.7 to −0.3) and after the intervention (−0.4% per year −0.6 to −0.1) was identified (shown in Table 1 and Figure 1).

In supplementary analyses, we identified no immediate difference or increase in trend when stratifying on kidney function, type of prophylaxis, age; nor when only considering initiation of statin treatment (shown in Table 1 and Figure 1). In individuals with a median eGFR below 15 ml/min/1.73 m^2 not on dialysis, a linear increase in the prevalence proportion was seen from 27% at the beginning of the study period to 35% at the end of the study period (figure), but no difference in the pre-intervention (+1.3% per year, −2.7 to 5.3) and post-intervention trend (+1.2 per year, −4.2 to 6.6).

The 180-day prevalence of statin use was slightly higher at the beginning (48%) and at end of the study period (49%), compared to the 90-day prevalence.

4 | DISCUSSION/CONCLUSION

In this population-based study including all patients with a median eGFR below 60 ml/min/1.73 m^2 living on the island of Funen, Denmark, we could not identify an increased prevalence of statin use up to 2 years after the release of the KDIGO guideline.

Few studies have investigated the impact of the KDIGO guideline on statin treatment in selected patient populations: In a Spanish single-centre study from a tertiary nephrology outpatient clinic, 60% of patients who were eligible to treatment with statins according to the KDIGO guidelines, received treatment. This proportion is larger compared to both the 90- and 180-day period prevalence we found at the end of the study period (40% and 49%). This difference may be explained by increased KDIGO guideline awareness among nephrologists compared to other clinicians. A large German study estimated that guideline implementation would increase the statin prescriptions from 47% to 88% in a hospital setting.[7]

Our study is one of the first to investigate the effect of KDIGO guideline implication using routinely collected health data from an unselected group of patients. Further, the Danish health-care registers are renowned for their high coverage, validity and quality.[8,11] Previous studies have investigated nephrology outpatients, who may not be representative of the entire KDIGO guideline target population,[6,7] as less than 10% of patients with CKD are seen by a nephrologist.[12] Our cohort includes both CKD patients who are followed by nephrologists and non-followed patients.

Apart from its role in cardiovascular events, statins may have an influence on kidney function. Both protective[13] as well as detrimental effects on renal function have been described.[14] A recent review found that statins have a role in the prevention of cardiovascular disease; yet, there is not enough evidence for a role of statins in kidney protection.[15] Future studies should assess the effects of chronic statin therapy on kidney function, especially in elderly and diabetic patients with CKD.

Limitations: Our study is limited by the lack of information on why patients were not treated with statins. Polypharmacy, age or side effects may have played a role.[16] The different statins have different side effects, and specific drug interactions can cause additional side effects.[17] A detailed discussion of potential statin toxicity is out of the scope of this short communication but can be reviewed in recent articles by Serban, Ward and Mollazadeh.[18–20]

Further, the study does not account for whether individuals were followed as outpatients. Our choice of effect measure (period prevalence) is affected by both the initiation and discontinuation of statin treatment and may therefore be less sensitive to guideline changes. However, we assumed that the primary objective of the guideline was to increase the prevalence of statin use among patients with an eGFR <60 ml/min/1.73 m^2. Further, the sensitivity analysis on the incidence of statin use yielded comparable results to the main analysis.

In conclusion, we found no evidence of an increased prevalence of statin use after the KDIGO guideline publication for lipid management in patients 50 years or older with an eGFR below 60 ml/min/1.73 m^2.

Ensuring dissemination of the KDIGO guideline beyond nephrology specialists may improve evidence-based prophylactic statin treatment in a broader spectrum of CKD patients. The next step is to define clinical settings where the guidelines are insufficiently adhered to and to identify barriers for implementation in everyday clinical practice.

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CONFLICT OF INTEREST

JDK has no conflicts of interest to declare. MN has no conflicts of interest to declare. FB has no conflicts of interest to declare. HS reports personal fees from Bristol-Myers-Squibb, personal fees from Novartis and personal fees from Roche, outside the submitted work.

He has personally received fees from Atrium education, the Danish Pharmaceutical Industry Association, for teaching a pharmacoepidemiology course. PD has no conflicts of interest to declare. DH has no conflicts of interest to declare. LCL reports participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma with funds paid to the institution where he was employed.

DATA AVAILABILITY STATEMENT

Aggregated time series data used to obtain regression coefficients for the main analysis can be found in the supporting information. Individual level data used to estimate 95% confidence intervals could not be published due to Danish privacy legislation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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