Implementation of the KDIGO guideline on lipid management requires a substantial increase in statin prescription rates

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The KDIGO guideline on lipid management in adult patients with chronic kidney disease (CKD) reflects a paradigm shift as proposals for statin use are based on cardiovascular risk rather than cholesterol levels. Statin use is now universally recommended in CKD patients 50 years and older, assuming a 10-year risk of coronary heart disease (CHD) of over 10%. Specific comorbidities or formal risk calculation are required for younger patients. It is unknown to which extent these new guidelines differ from previous practice. Here we analyzed statin use in the German Chronic Kidney Disease study of 5217 adult patients with moderately severe CKD under nephrological care enrolled shortly before publication of the new guideline. Accordingly, 407 patients younger than 50 years would be eligible for statins compared with the 277 patients treated so far, and all 4224 patients 50 years and older would be eligible compared with the 2196 already treated. Overall, guideline implementation would almost double statin prescription from 47 to 88%. Among patients 50 years and older currently not on a statin, an estimated 10-year CHD and atherosclerotic event risks over 10% were present in 68% and 82%, respectively. Thus, implementation of the new lipid guideline requires a substantial change in prescription practice, even in CKD patients under nephrological care. Based on comorbidities and risk estimates, the universal recommendation for statin use in CKD patients 50 years and older appears justified.

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Dyslipidemia is highly prevalent and contributes to the high rate of cardiovascular (CV) complications in patients with chronic kidney disease (CKD).[1–3] In 2003, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) published the first guideline addressing lipid therapy in CKD patients. This guideline recommended a low-density lipoprotein (LDL) cholesterol target of <100 mg/dl in CKD patients on the basis that CKD was viewed as a coronary heart disease (CHD) risk equivalent. It was recommended to treat with a statin whenever this LDL cholesterol target could not be reached with lifestyle changes. However, at the time of publication, solid evidence from clinical trials that such an approach would improve outcomes in CKD patients was not available. In fact, two large randomized trials failed to demonstrate a benefit from statin therapy in patients on dialysis.[4,5] For some time, this created uncertainty regarding lipid therapy in CKD patients. However, the subsequent Study of Heart and Renal Protection (SHARP) showed a clear benefit of a combined treatment with simvastatin and ezetimibe in a large cohort of CKD patients, with renal function ranging from mildly impaired to dialysis-dependent.[6] This study reinstated statin therapy as one of the few means demonstrated to improve outcomes in CKD patients.[7]

Recently, the American College of Cardiology (ACC) and the American Heart Association (AHA) jointly published their new guideline on lipid therapy.[8] This guideline represents a paradigm shift away from a 'lipid-focused' view, towards a risk-based approach deriving the decision to use a statin from individualized CV risk assessment. Statin therapy is now recommended for patients with already established atherosclerotic CV disease (considered at high risk for future events),

Table 1 | Characteristics of patients with and without statin therapy

Parameter	Patients with statin, $N = 2473$	Patients without statin, $N = 2744$
Age (median, IQR) (years)	66 (58–70)	61 (49–69)
Male sex, *n* (%)	1644 (66.5%)	1488 (54.2%)
Hypertension, *n* (%)	2445 (98.9%)	2571 (93.7%)
Diabetes mellitus, *n* (%)	1139 (46.1%)	703 (25.6%)
BMI (median, IQR) (kg/m^2)	29.9 (26.6–34.2)	28.1 (24.8–32.2)
Current smoking, *n* (%)	371 (15.0%)	457 (16.7%)
Coronary heart disease, *n* (%)	796 (32.2%)	243 (8.9%)
Prior MI, *n* (%)	471 (19.1%)	112 (4.1%)
CABG, *n* (%)	302 (12.2%)	45 (1.6%)
PCI, *n* (%)	573 (23.2%)	170 (6.2%)
Cerebrovascular disease, *n* (%)	354 (14.3%)	156 (5.7%)
Prior stroke, *n* (%)	291 (11.8%)	139 (5.1%)
Carotid surgery, *n* (%)	93 (3.8%)	25 (0.9%)
Carotid intervention, *n* (%)	47 (1.9%)	13 (0.5%)
Peripheral vascular disease, *n* (%)	323 (13.1%)	170 (6.2%)
Heart failure, *n* (%)	576 (23.3%)	352 (12.8%)
Atrial fibrillation, *n* (%)	268 (10.9%)	212 (7.7%)
Diabetic nephropathy, *n* (%)	874 (35.3%)	534 (19.5%)
Vascular nephropathy, *n* (%)	1165 (47.1%)	992 (36.2%)
Systemic disease, *n* (%)	238 (9.6%)	374 (13.6%)
Primary glomerulopathy, *n* (%)	560 (22.6%)	625 (22.8%)
eGFR (median, IQR) (ml/min per 1.73 m^2)	45 (36–55)	48 (38–60)
Cystatin C (median, IQR) (mg/l)	1.49 (1.24–1.81)	1.38 (1.15–1.73)
UACR (median, IQR) (mg/g)	38.7 (36.4–41.0)	38.8 (36.5–41.1)
Total cholesterol (mg/dl)	196 ± 52	225 ± 50
HDL cholesterol (mg/dl)	51 ± 17	53 ± 19
LDL cholesterol (mg/dl)	103 ± 41	132 ± 41
Triglycerides (mg/dl)	210 ± 131	189 ± 125
CRP (median, IQR) (mg/l)	2.29 (1.04–4.82)	2.29 (1.02–5.23)
Phosphate (median, IQR) (mg/l)	1.10 (0.96–1.24)	1.10 (0.97–1.23)
Uric acid (median, IQR) (mg/dl)	7.22 (6.12–8.47)	6.96 (5.75–8.1)
Hemoglobin (median, IQR) (g/dl)	13.6 (12.6–14.7)	13.6 (12.6–14.7)
HbA1c (median, IQR) (%)	6.2 (5.6–6.8)	5.9 (5.6–6.3)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CKD-EPI, Chronic Kidney Disease-Epidemiology; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention, UACR, urinary albumin-to-creatinine ratio.
Values are mean ± s.d., unless indicated otherwise. Missing values were <5% for all parameters presented.

or an estimated 10-year risk for an atherosclerotic CV event >7.5%. For estimation of risk, new risk equations were developed using data pooled from several large cohort studies.[9]

In parallel, Kidney Disease: Improving Global Outcomes (KDIGO) also developed a new 'Clinical Practice Guideline for Lipid Management in CKD'.[10,11] Similar to the ACC-AHA guideline, the new KDIGO guideline on lipid management adopts a risk-based approach for statin indication and refrains from recommending specific LDL cholesterol targets. The KDIGO guideline even goes a step further in simplifying treatment decisions: CKD patients ⩾50 years of age are considered at sufficiently high risk for a CV event (>10% risk of manifest CHD over 10 years) to justify statin therapy without the need for applying any formal risk calculation in individual patients. In patients 18–49 years of age, statin therapy is recommended for those with known CHD (prior myocardial infarction or coronary revascularization), diabetes mellitus, or prior ischemic stroke. Only if none of these comorbidities are present, formal risk assessment is recommended to guide therapy in CKD patients 18–49 years of age, with a 10-year risk of CHD >10% justifying statin therapy. By simplifying the decision processes, the guideline workgroup aimed to facilitate implementation of the recommendations into clinical practice.

How these recommendations differ from practice and the impact this new KDIGO guideline should have on statin prescription rates is currently unknown. We therefore analyzed statin use before publication of the novel KDIGO lipid guideline in the German CKD (GCKD) study, the worldwide largest cohort study of CKD patients under nephrological care.[12,13] Implementation of the new KDIGO lipid guideline was simulated based on prevalent comorbidities and CV risk estimates.

RESULTS

Clinical characteristics of patients with versus without statin therapy

In the GCKD cohort, 2473 (47%) out of the 5217 patients received statins, whereas 2744 (53%) did not receive statin therapy. Clinical characteristics of patients with and without statin therapy are presented in Table 1. Patients who received statin therapy were older, were more frequently male, had higher body mass index, slightly higher rate of hypertension,

Table 2 | Application of the new KDIGO guideline to the GCKD cohort

	Previous practice		Application of new guideline	
Age group (years)	With statin	Without statin	Additional condition required	Newly eligible for statin
⩾50				
N = 4224 (81% of GCKD cohort)	2196	2028	Not applicable	2028
18–49				
N = 992 (19% of GCKD cohort)	277	715	CHD	13
			Diabetes mellitus	52
			CHD and diabetes mellitus	3
			Prior ischemic stroke	9
			Individual estimated risk of CHD >10%	53
Total	2473 (47% of GCKD cohort)	2743 (53% of GCKD cohort)		2158 (41% of GCKD cohort)

Abbreviations: CHD, coronary heart disease; GCKD cohort, German Chronic Kidney Disease cohort; KDIGO, Kidney Disease: Improving Global Outcomes.

and substantially higher rate of diabetes. Correspondingly, uric acid and hemoglobin A1c (HbA1c) values were higher in those on statins. C-reactive protein, phosphate, and hemoglobin values were similar. Patients on statins had much higher prevalence of established CV disease, including CHD, cerebrovascular disease (CeVD), peripheral vascular disease (PVD), and heart failure. A renal diagnosis of diabetic nephropathy or vascular nephropathy was more common, whereas systemic disease associated with renal dysfunction was less common in those on statins. Glomerular filtration rate (GFR) estimated with the CKD-Epidemiology (CKD-EPI) formula[14] and, in addition, determined via cystatin C levels was slightly lower in those on statins. As expected, total and LDL cholesterol were lower in patients on statins. Among those treated with a statin, 1147 (46%) had LDL cholesterol levels ⩾100 mg/dl, and did not reach the recommended target level of <100 mg/dl of the KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in CKD.

Application of the novel KDIGO guideline to the GCKD cohort

According to the novel KDIGO guideline, all patients with CKD who are ⩾50 years of age have an indication for statin therapy, regardless of the presence or absence of other comorbidities. In the GCKD study, 4224 of 5217 patients fall in this age group (81% of the total cohort). At the time of the baseline visit, before publication of the KDIGO guideline, 2196 of these 4224 patients (52%) were receiving statin therapy (Table 2). According to the KDIGO guideline, all 2028 patients not on statins (48% of patients ⩾50 years of age, corresponding to 39% of the total GCKD cohort) would now qualify for statin therapy (Table 2).

The presence of additional comorbidities or individual risk calculations is required for patients 18–49 years of age to recommend statin therapy according to the KDIGO guideline. In the GCKD cohort, 992 of 5217 patients belong to this age group (19% of the total GCKD cohort). Two hundred and seventy-seven of these 992 patients (28%) received statin therapy (Table 2 and Figure 1). Among those not yet receiving statin therapy according to the new KDIGO guideline, 1% ($n = 13$ of 992) would qualify because of CHD, 5% ($n = 52$) because of diabetes, 0.3% because of CHD and diabetes mellitus ($n = 3$), and 1% ($n = 9$) because of prior ischemic stroke. Five percent ($n = 53$) do not have any of the aforementioned conditions (CHD, diabetes, or prior ischemic stroke) but an estimated 10-year CHD risk of >10% according to the Framingham-CHD risk equations. Therefore, they would also qualify for statin therapy according to the new KDIGO guideline. Thus, the overall proportion of patients 18–49 years of age eligible for statin therapy would increase from 28% (those already treated) to 41%, whereas 59% would remain without indication. Considering the entire GCKD cohort, implementing the recommendations of the new guideline would increase statin prescription rate from 47 to 88%.

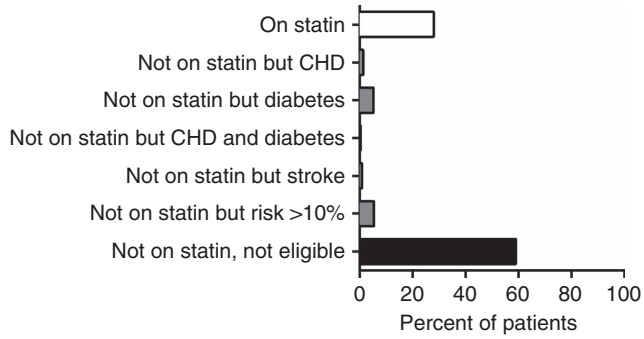

Figure 1 | Application of the new Kidney Disease: Improving Global Outcomes (KDIGO) guideline to patients 18–49 years in the German Chronic Kidney Disease (GCKD) cohort.

Distribution of atherosclerotic event risk in patients ⩾50 years of age not treated with a statin

The assumption that many CKD patients ⩾50 years of age will have an estimated 10-year risk for CHD of >10% had an important role in the development of the novel KDIGO guideline. To examine the validity of this assumption, we

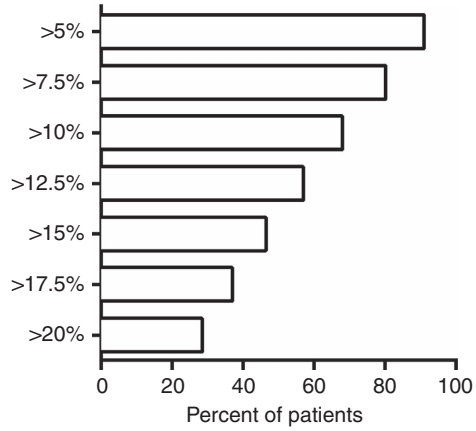

Figure 2 | Percent of patients ⩾50 years in the German Chronic Kidney Disease (GCKD) cohort exceeding various thresholds of 10-year risk for coronary heart disease according to the Framingham-coronary heart disease (CHD) risk equations.

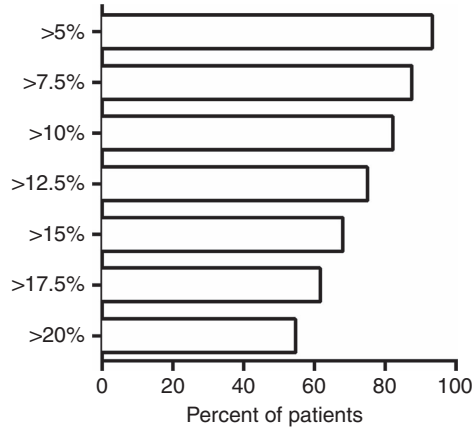

Figure 3 | Percent of patients ⩾50 years in the German Chronic Kidney Disease (GCKD) cohort exceeding various thresholds of 10-year risk of an atherosclerotic event according to the American College of Cardiology and the American Heart Association (ACC-AHA) risk equations.

calculated the percent of subjects exceeding various risk thresholds in the patients ⩾50 years not treated with a statin, using the Framingham-CHD risk equations (Figure 2).[15] Sixty-eight percent of patients ⩾50 years of age not on a statin had an estimated 10-year risk of CHD of >10% at the time of enrollment. In addition, we also calculated atherosclerotic event risk according to the new ACC-AHA Pooled Risk Equations.[9] Eighty-two percent of patients ⩾50 years of age not on a statin had an atherosclerotic event risk >10 and 88% had an atherosclerotic event risk of >7.5%, which is the threshold for statin therapy recommended by the new ACC-AHA guidelines (Figure 3). Furthermore, even in those allocated to a lower risk group according to formal atherosclerotic event risk calculation, some patients had diabetes or established CV disease, thus qualifying for statin therapy (Table 3). In consequence, these data suggest that the assumption of a high CV risk in CKD patients ⩾50 years not yet receiving statin therapy is valid.

DISCUSSION

This analysis in a large cohort of CKD patients under nephrological care revealed that implementation of the new KDIGO lipid guideline requires a substantial increase in the number of patients with statin prescription: only about half of patients ⩾50 years in whom statin therapy is now universally recommended were prescribed statins before publication of the guideline. The rationale behind the uniform recommendation of statin therapy in all CKD patients ⩾50 years without further consideration of comorbidities and without formal risk assessment was the assumption that many of these patients will have a 10-year CHD risk >10%. Given the concern of 'overtreatment,' we tested this assumption in the GCKD cohort, and found that 68% of the patients in this age group not already on statin therapy had an estimated CHD risk of >10% according to the Framingham-CHD risk equations. However, the Framingham instrument is less accurate in predicting CHD events in CKD patients compared with its use in the non-CKD population.[16] Thus, as a second tool, we used the new ACC-AHA Pooled Risk Equations to calculate risk of atherosclerotic events, which is the main driver for statin indication in the new ACC-AHA guideline. Recent data demonstrated that this new tool predicts atherosclerotic event rates accurately in CKD and non-CKD patients.[17,18] Applying the ACC-AHA Pooled Risk Equations, 82% of patients ⩾50 years of age currently not on a statin had an atherosclerotic event risk >10 and 88% a risk of >7.5%, which is the threshold for recommending statin therapy in the new ACC-AHA guideline. As expected, we found an increasing number of CV comorbidities with increasing atherosclerotic event risk. In addition, some patients also had diabetes and/or established CV disease despite being allocated to a lower CV risk category, and would also merit statin therapy according to the new ACC-AHA and KDIGO guidelines. Of note, some patients allocated to lower risk categories had albuminuria, which is not a component of the ACC-AHA Pooled Risk Equations, and their true CV risk might be greater. Thus, based on comorbidities and CV risk, the universal recommendation for statin use in CKD patients ⩾50 years appears justified. In addition, we found that some of the younger CKD patients (13%), who have not been prescribed a statin so far, qualify for treatment according to the new guideline, mostly because of the presence of diabetes or because of their individually estimated event risk.

There are at least three reasons why the observed practice differs substantially from the recommendations of new guidelines: (i) Novel evidence that influenced guideline recommendations may not yet have been implemented in clinical practice. (ii) Guideline workgroups may have interpreted existing evidence in a novel way that differs from the interpretation that has previously determined practice. (iii) There are hurdles that have so far hampered certain measures despite sufficient evidence. All three aspects may

Table 3 | Characteristics of patients ⩾50 years of age not on statin therapy according to ACC-AHA atherosclerotic event risk (*n* = 1829, *n* = 199 missing)

	10-year risk for atherosclerotic CV event							
Parameter	⩽5% *N* = 122	>5–⩽7.5% *N* = 106	>7.5–⩽10% *N* = 98	>10–⩽12.5% *N* = 132	>12.5–⩽15% *N* = 126	>15–⩽17.5 *N* = 116	>17.5–⩽20% *N* = 128	>20% *N* = 1001
Age (median, IQR) (years)	54 (52–57)	57 (53–62)	59 (54–65)	62 (57–67)	63 (58–68)	63 (57–69)	66 (61–71)	69 (66–73)
Male sex, *n* (%)	11 (9)	24 (23)	30 (31)	55 (42)	53 (42)	60 (52)	65 (51)	748 (75)
Hypertension, *n* (%)	100 (82)	95 (90)	85 (87)	125 (95)	118 (94)	112 (97)	124 (97)	988 (99)
Diabetes mellitus, *n* (%)	3 (2)	6 (6)	7 (7)	11 (8)	11 (9)	17 (15)	17 (13)	505 (50)
BMI (median, IQR) (kg/m^2)	27 (23–30)	28 (24–31)	27 (23–30)	28 (25–31)	29 (25–32)	28 (25–31)	28 (25–33)	30 (26–33)
Current smoking, *n* (%)	12 (10)	12 (11)	10 (10)	14 (11)	26 (21)	22 (19)	15 (12)	118 (12)
CHD, *n* (%)	5 (4)	3 (3)	6 (6)	9 (7)	8 (6)	6 (5)	8 (6)	151 (15)
CeVD, *n* (%)	1 (1)	2 (2)	8 (8)	8 (6)	6 (5)	6 (5)	7 (5)	80 (8)
PVD, *n* (%)	2 (2)	2 (2)	4 (4)	5 (4)	10 (8)	7 (6)	8 (6)	94 (9)
Any of CHD, CeVD, and PVD, *n* (%)	7 (6)	6 (6)	15 (15)	17 (13)	21 (17)	15 (13)	19 (15)	268 (27)
Diabetic nephropathy, *n* (%)	2 (2)	6 (6)	4 (4)	14 (11)	10 (8)	15 (13)	16 (13)	383 (38)
Estimated GFR by CKD-EPI formula (median, IQR) (ml/min per 1.73 m^2)	53 (42–63)	49 (41–60)	49 (41–59)	47 (39–58)	46 (35–55)	47 (38–55)	46 (35–58)	44 (35–53)
Urinary albumin-to-creatinine ratio (median, IQR) (mg/g)	39 (37–41)	39 (37–41)	39 (37–42)	39 (37–41)	39 (37–41)	38 (36–40)	39 (38–41)	39 (37–41)
Total cholesterol (mg/dl)	218 ± 40	226 ± 32	226 ± 38	225 ± 43	225 ± 37	224 ± 42	227 ± 42	220 ± 39
HDL cholesterol (mg/dl)	64 ± 15	57 ± 15	58 ± 15	57 ± 17	55 ± 14	55 ± 17	53 ± 14	47 ± 14
LDL cholesterol (mg/dl)	126 ± 34	135 ± 28	134 ± 36	136 ± 35	137 ± 34	132 ± 37	137 ± 35	129 ± 33
Triglycerides (mg/dl)	131 ± 63	164 ± 83	160 ± 74	157 ± 75	160 ± 73	183 ± 102	176 ± 83	213 ± 120

Abbreviations: ACC-AHA, American College of Cardiology and the American Heart Association; BMI, body mass index; CeVD, cerebrovascular disease; CHD, coronary heart disease; CKD-EPI, Chronic Kidney Disease-Epidemiology; CV, cardiovascular; GFR, glomerular filtration rate; IQR, interquartile range; PVD, peripheral vascular disease.
Values are mean ± s.d., unless indicated otherwise. *N* = 199 missing values (when ⩾1 parameter required for risk calculation was not available).

have a role for the huge discrepancy between guideline recommendations and practice patterns observed in the current analysis.

With respect to new evidence, the KDIGO lipid guideline recommendations were to large extent influenced by the results of the SHARP study, which were first made public in November 2010, when recruitment into the GCKD study was already ongoing for half a year. Moreover, although SHARP demonstrated a reduction in vascular events, this did not translate into a survival benefit.[6] Although the study may have been underpowered to determine effects on mortality, the lack of an effect on survival may nevertheless have reduced the perceived importance. In addition, SHARP tested the combination of ezetimibe plus simvastatin, perhaps resulting in some uncertainty on the relevance of either drug.

As regards the interpretation of existing evidence, the novel guidelines for lipid management in the general population (ACC-AHA) and for patients with CKD (KDIGO) represent a true paradigm shift, with less emphasis on LDL cholesterol values, and more emphasis on individual CV risk in guiding the decision whether to recommend statin therapy.[8,10] In addition, both the ACC-AHA and KDIGO guidelines no longer recommend follow-up measurements of lipid levels as there is no data supporting treatment escalation to achieve specific LDL cholesterol targets.[19] One aspect of this decision was that there is substantial within-person variability in LDL cholesterol measurements, which reduces the clinical utility of follow-up measuremens.[20,21] In CKD patients, an additional problem is that there is lack of safety data of high-intensity statins regimens, further questioning the usefulness of follow-up measurements.

Concerning implementation, several hurdles clearly exist, although some of them might be overcome if addressed adequately. Several methods for enhancing the implementation of clinical practice guidelines have been evaluated in different clinical settings. Professional education targeting primary care has been demonstrated as effective in increasing CV medication including statins in CKD patients.[22] The vast majority of CKD patients are managed in primary care and therefore targeting this health-care sector will be crucial for guideline implementation. In some settings, disposition of nurse practitioners checking whether the patients' medication is in line with guideline-recommended therapy has been shown to improve quality of care in patients with CKD.[23] A further method might be to incorporate calculations of CV risk into electronic health records. Another important aspect concerns reimbursement. In Germany, costs of statin therapy are generally reimbursed in the setting of secondary but not primary CV disease prevention. As a consequence, statin prescriptions for primary prevention in CKD patients have not infrequently led to queries by the health insurance company in the past. Increasing the awareness for the fact that statins are now widely recommended for primary prevention in CKD patients is not only required in the medical profession but also in the health insurance sector. It is also important to recognize that the medication burden of CKD patients is substantial because of a large number of comorbidities. In the GCKD cohort, we found that the median number of prescribed medications is 8 (unpublished observations). Thus, physicians may be reluctant to further increase the number of prescribed drugs. Against this background, physicians need to focus on those treatments with clear clinical benefit, and fixed medication combinations might be helpful to improve adherence to therapy.

It is important to note that our study was conducted in patients under nephrological care. Comparison with reported data from other CKD cohorts suggest, however, that the statin prescription rate does not differ substantially among patients

with and without specialized renal care. Another study in patients under nephrological care from Spain reported a statin prescription rate of 55%,[24] which resembles the 47% statin prescription rate in GCKD. Data from the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS), conducted in the primary care setting in the United States, demonstrate a similar statin prescription rate of 50% in CKD patients $\geqslant 50$ years.[17] In CKD-JAC from Japan, also a primary care study, a statin prescription rate of 40% was reported.[25] An Australian study in primary care reported a statin prescription rate of 54% in CKD patients $\geqslant 55$ years.[26] Interestingly, statins were prescribed more frequently in those with more advanced renal impairment, who had a greater prevalence of established CV disease. The population-based Alberta Kidney Disease Network reported statin use in only 29% of subjects with an eGFR between 15 and 59.9 ml/min ($N = 47\,092$, mean age 70.5 ± 11.5 years).[2] However, CV disease was reported in only 7% of these subjects. In summary, therefore, the new KDIGO guideline requires a change of practice patterns in both primary and nephrological care settings.

Implementation of the new KDIGO guideline will also have health economic implications. A reduction in the risk of a major atherosclerotic event with lipid-lowering therapy similar to that observed in the SHARP trial would correspond to the prevention of 30–40 major atherosclerotic events per 1000 patients treated for 5 years.[6] The absolute benefit would be even larger in CKD patients with a history of CHD. These patients were excluded from SHARP, but their absolute CV risk is two or three times higher.[6] The use of widely available, low-cost generic statins is likely to be cost-effective (Schlackow *et al.* Lifetime Benefits and Cost-Effectiveness of LDL-Cholesterol Lowering in Chronic Kidney Disease: Results From the Study of Heart and Renal Protection (SHARP). *J Am Soc Nephrol* 2014; 25: 276A (abstract)).[27] In Germany, 5 years of therapy with simvastatin 40 mg at a price of 23 cents would result in net costs of €420 per major atherosclerotic event avoided, assuming similar hospital costs as in SHARP (Dr Borislava Mihaylova, Health Economics Research Centre at the University of Oxford, UK, personal communication). Based on these data, implementation of new KDIGO guideline should also be beneficial from a public health perspective.

Several limitations apply to the current analysis. Patients were interviewed about their drug intake and prescription was not formally assessed. However, the overall number and spectrum of medications that were recorded do not suggest substantial underreporting. Second, we have no information on patients who previously had been prescribed a statin and discontinued because of side effects. Although such statin-intolerant patients could slightly reduce the difference between current practice and guideline recommendations, we believe that the gap would in any case remain very substantial. Third, we have no information on adherence to prescribed medication. Finally, we had to assume that those patients younger than 50 years who are currently on a statin would also have an indication according to the new KDIGO guideline. We would need off-treatment cholesterol levels to calculate the exact number of patients who would remain eligible, but these data are not available. However, the fact that patients currently prescribed a statin had much higher rates of diabetes and higher rates of CV comorbidities suggest that most of these patients would remain eligible when applying the new guideline.

In summary, slightly less than half of patients (47%) in the GCKD study cohort were found to be on statin therapy at baseline. Apparently, established atherosclerotic CV disease and diabetes were the main drivers for the decision to prescribe statin treatment in our cohort. As the key finding of our study, implementation of the KDIGO guideline would almost double the number of patients with statin prescriptions. Future analysis will have to investigate the extent to which this implementation is achieved after guideline publication and the associated benefit.

MATERIALS AND METHODS

The methodology and baseline data of the GCKD study have previously been reported in detail.[12,13] Briefly, the GCKD study is a prospective, observational cohort study conducted within a network of 9 regional centers and 159 study sites throughout Germany. GCKD enrolled 5217 Caucasian CKD patients under specialized care on the basis of two inclusion strata: eGFR 30–60 ml/min $\times$ 1.73 m^2 or overt proteinuria (urinary albumin/creatinine >300 mg/g, albuminuria >300 mg per day, urinary protein/creatinine >500 mg/g, or proteinuria >500 mg per day) in the presence of an eGFR >60 ml/min $\times$ 1.73 m^2. Patients after solid organ or bone marrow transplantation, with active malignancy within 24 months before screening, heart failure NYHA IV, legal attendance, or inability to provide consent could not take part in the study. The GCKD study has been approved by local ethics committees and registered in the national registry for clinical studies (DRKS 00003971).

The current analysis is based on the baseline visit, which was conducted between April 2010 and March 2012, and thus 20–43 months before publication of the new KDIGO lipid guideline in November 2013.[10] Clinical measurements were performed and information was collected on sociodemographic factors, medical and family history, and medications (prescribed drugs and over-the-counter drugs) by a trained and certified study team. The renal diagnosis was obtained from the patients' nephrologists. Diabetes mellitus was defined as the use of antidiabetic medication or an HbA1c level $>6.5\%$. Hypertension was defined as the use of antihypertensive medication, or systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg, from an average of three readings. CHD was defined as prior myocardial infarction, percutaneous coronary angioplasty, or coronary artery bypass grafting. CeVD was defined as prior stroke (ischemic or hemorrhagic), carotid intervention, or carotid surgery. PVD was defined as prior percutaneous angioplasty, bypass surgery, other surgical revascularization procedure, or amputation. Data collection procedures were monitored by an internal quality control panel that was advised by external reviewers. Patient interviews were recorded and audited for quality control.

Every medication currently taken by a patient was recorded, and active ingredients were coded using the latest ATC codes (http://www.wido.de/amtl_atc-code.html, version for 2013). The use of a statin was based on the codes C10AA01 (simvastatin), C10AA02 (lovastatin),

C10AA03 (pravastatin), C10AA04 (fluvastatin), C10AA05 (atorvastatin), C10AA06 (cerivastatin), C10AA07 (rosuvastatin), and C10AA08 (pitavastatin). We also included the codes for available combinations of medications containing a statin: C10BA01 (lovastatin and nicotinic acid), C10BA02 (simvastatin and ezetimibe), C10BA03 (pravastatin and fenofibrate), C10BX01 (simvastatin and acetylsalicylate), C10BX02 (pravastatin and acetylsalicylate), C10BX03 (atorvastatin and acetylsalicylate), and C10BX04 (simvastatin, acetylsalicylate, and ramipril).

Laboratory measurements

Plasma, serum, blood, and spot-urine samples were collected, processed, and shipped frozen to a central laboratory for routine clinical chemistry of a core set of parameters (Synlab, Heidelberg, Germany). Hemoglobin and HbA1c measurements were performed locally (Central Lab of the University Hospital Erlangen, Erlangen, Germany). Serum creatinine was analyzed using an IDMS-traceable methodology. GFR values were calculated using the CKD-EPI formula.[14] Cystatin C and albumin were measured by immunoturbidimetric assays.

Calculation of CHD risk (Framingham) and atherosclerotic event risk (ACC-AHA)

We calculated 10-year risk of manifest CHD using the Framingham-CHD risk equations.[15] In line with recommendations, Framingham-CHD risk calculation was performed only in patients 30–74 years of age, systolic blood pressure 95–185 mm Hg, total cholesterol 135–330 mg/dl, high-density lipoprotein cholesterol 25–99 mg/dl, and in the absence of established CV disease. Where indicated, we additionally used the novel ACC-AHA Pooled Risk Equations to calculate 10-year atherosclerotic event risk.[9] Use of these equations is only recommended in patients 40–79 years of age, with total cholesterol 130–320 mg/dl, high-density lipoprotein cholesterol 20–100 mg/dl, and systolic blood pressure 90–200 mm Hg.

Statistics

SAS Software Version 9.2 and R Version 3.1.1 were used for statistical analysis. Data are presented as means with s.d. or medians with interquartile ranges for continuous variables, and frequency distributions with percentages for categorical variables. Missing values occurred when a question was not answered on the case report form, a physical test or a laboratory test was not performed, or the result was not entered into the central data bank. The statistical analysis of each variable was based on the available values only.

DISCLOSURE

KUE and CW are members of the KDIGO executive board. CW was work group cochair and FK work group member of the KDIGO Clinical Practice Guideline for Lipid Management in CKD. MPS, SH, SIT, MS, JN, GS, MB, SB-A, and VK have no disclosures pertinent to the content of this article.

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