Implementation of the KDIGO Guideline on Lipid Management would require substantial increase in statin prescription: an analysis from the German Chronic Kidney Disease (GCKD) cohort

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On behalf of the GCKD investigators

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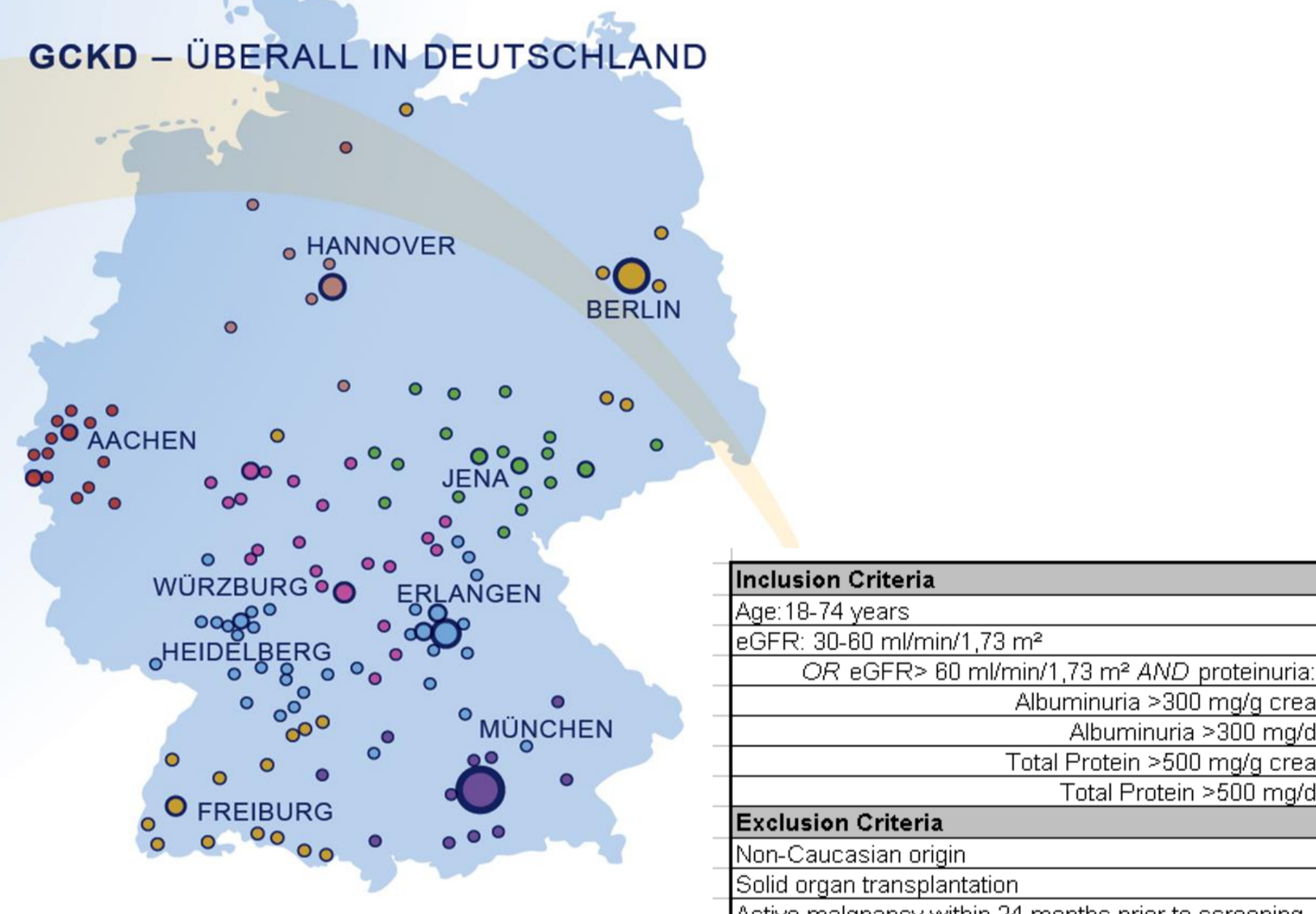
Background/Aims

The novel KDIGO guideline on lipid management in adult patients with chronic kidney disease (CKD) reflects a paradigm shift as recommendations for statin use are now based on cardiovascular (CV) risk rather than cholesterol levels.

Statin use is now universally recommended in CKD patients ≥ 50 yrs, assuming a 10-year risk of coronary heart disease (CHD) of >10%, while specific co-morbidities or formal risk calculation are required for younger patients.

It is unknown to which extent these new recommendations differ from practice. We analyzed statin use in the German Chronic Kidney Disease (GCKD) study, which enrolled 5217 adult patients with moderately severe CKD under nephrological care shortly before publication of the new guideline and simulated its implementation.

Methods

The German Chronic Kidney Disease (GCKD) Study is a prospective observational national cohort study conducted within a network of 9 regional centers and 159 study sites throughout Germany. It has enrolled patients with CKD of various aetiologies who are under nephrological care and aims to follow them for up to ten years. Patient recruitment was organized through a network of academic nephrology centres collaborating with practising nephrologists throughout the country. All patient data on disease history, demographics and medication is collected by trained and certified nurses. Active ingredients of medications were coded using the latest ATC codes (http://www.wido.de/amtl_atc-code.html, version for 2013). **The current analysis is based on the baseline visit, which was conducted between April 2010 and March 2012 and thus 20-43 months prior to publication of the new KDIGO lipid guideline in November 2013.**

GCKD – ÜBERALL IN DEUTSCHLAND

Inclusion Criteria
Age 18-74 years
eGFR 30-60 ml/min/1.73 m²
OR eGFR> 60 ml/min/1.73 m² AND proteinuria
Albuminuria >300 mg/g crea
Albuminuria >300 mg/d
Total Protein >500 mg/g crea
Total Protein >500 mg/d
Exclusion Criteria
Non-Caucasian origin
Solid organ transplantation
Active malignancy within 24 months prior to screening

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. In line with recommendations, Framingham-CHD risk calculation was performed only in patients 30-74 years of age, systolic BP 95-185 mmHg, total cholesterol 135-330 mg/dl, HDL cholesterol 25-99 mg/dl, and in the absence of established CV disease. We also used the novel ACC-AHA Pooled Risk Equations to calculate 10-year atherosclerotic event risk. Use of these equations is only recommended in patients 40-79 years of age, with total cholesterol 130-320 mg/dl, HDL cholesterol 20-100 mg/dl and systolic BP 90-200 mmHg.

Statistics

SAS Software Version 9.2 and R Version 3.1.1 were used for statistical analysis. Data are presented as means with standard deviation (SD) or medians with interquartile ranges (IQR) for continuous variables, and frequency distributions with percentages for categorical variables. Statistical comparisons between two groups were made by using t-tests and Mann-Whitney-U-tests for parametric and non-parametric data, respectively. Pearson's chi-squared test was applied for categorical variables. A two-sided P<0.05 was considered significant.

Patients with versus without current statin therapy

In the GCKD cohort, 2473 (47%) out of the 5217 patients received statins, whereas 2744 (53%) did not receive statin therapy. Patients who received statin therapy were older, had substantially higher rate of diabetes and established CV disease, including CHD, cerebrovascular disease, peripheral vascular disease and heart failure (**Table below**).

Parameter	Patients with statin N=2473	Patients without statin N=2744	P-Value
Age (median, IQR) – yrs	66 (58-70)	61 (49-69)	<0.001
Male sex – n (%)	1644/2473 (66.5%)	1488/2744 (54.2%)	<0.001
Hypertension – n (%)	2445/2473 (98.9%)	2571/2743 (93.7%)	<0.001
Diabetes mellitus – n (%)	1139/2473 (46.1%)	703/2744 (25.6%)	<0.001
BMI (median, IQR) - kg/m²	29.9 (26.6-34.2) N=2447	28.1 (24.8-32.2) N=2716	<0.001
Current smoking – n (%)	371/2467 (15.0%)	457/2734 (16.7%)	0.099
Coronary heart disease – n (%)	796/2472 (32.2%)	243/2743 (8.9%)	<0.001
Prior MI – n (%)	471/2472 (19.1%)	112/2743 (4.1%)	<0.001
CABG – n (%)	302/2472 (12.2%)	45/2743 (1.6%)	<0.001
PCI – n (%)	573/2472 (23.2%)	170/2743 (6.2%)	<0.001
Cerebrovascular disease – n(%)	354/2472 (14.3%)	156/2743 (5.7%)	<0.001
Prior stroke – n (%)	291/2472 (11.8%)	139/2743 (5.1%)	<0.001
Carotid surgery– n (%)	93/2472 (3.8%)	25/2743 (0.9%)	<0.001
Carotid intervention – n (%)	47/2472 (1.9%)	13/2472 (0.5%)	<0.001
Peripheral vascular disease – n (%)	323/2472 (13.1%)	170/2743 (6.2%)	<0.001
Heart failure – n (%)	576/2472 (23.3%)	352/2743 (12.8%)	<0.001
Atrial fibrillation - n (%)	268/2466 (10.9%)	212/2741 (7.7%)	<0.001
Diabetic nephropathy – n (%)	874/2473 (35.3%)	534/2744 (19.5%)	<0.001
Vascular nephropathy – n (%)	1165/2473 (47.1%)	992/2744 (36.2%)	<0.001
Systemic disease – n (%)	238/2473 (9.6%)	374/2744 (13.6%)	<0.001
Primary glomerulopathy – n (%)	560/2473 (22.6%)	625/2744 (22.8%)	0.909
eGFR (median, IQR) - ml/min/1.73m²	45 (36-55) N=2447	48 (38-60) N=2714	<0.001
Cystatin C (median, IQR) – mg/l	1.49 (1.24-1.81) N=2471	1.38 (1.15-1.73) N=2738	<0.001
UACR (median, IQR) – mg/g	38.7 (36.4-41.0) N=2446	38.8 (36.5-41.1) N=2714	0.146
Total cholesterol (mg/dl)	196±52 (N=2444)	225±50 (N=2711)	<0.001
HDL cholesterol (mg/dl)	51±17 (N=2443)	53±19 (N=2708)	<0.001
LDL cholesterol (mg/dl)	103±41 (N=2442)	132±41 (N=2708)	<0.001
Triglycerides (mg/dl)	210±131 (N=2443)	189±125 (N=2707)	<0.001
CRP (median, IQR) - mg/l	2.29 (1.04-4.82) N=2446	2.29 (1.02-5.23) N=2715	0.596
Phosphate (median, IQR) - mg/l	1.10 (0.96-1.24) N=2471	1.10 (0.97-1.23) N=2737	0.513
Uric acid (median, IQR) - mg/dl	7.22 (6.12-8.47) N=2447	6.96 (5.75-8.1) N=2715	<0.001
Hemoglobin (median, IQR) - g/dl	13.6 (12.6-14.7) N=2463	13.6 (12.6-14.7) N=2647	0.209
HbA1c (median, IQR) - %	6.2 (5.6-6.8) N=2368	5.9 (5.6-6.3) N=2654	<0.001

Values are mean ± SD unless indicated otherwise

Application of the novel KDIGO guideline to the GCKD cohort

According to the novel KDIGO guideline, all 2028 patients ≥ 50 yrs not on statins (48% of patients ≥ 50 of age), would now qualify for statin therapy (**Table below**). In patients 18-49 years of age, the presence of additional co-morbidities or individual risk calculation are required to recommend statin therapy according to the KDIGO guideline. 277 of these 992 patients (28%) received statin therapy. Among those not yet receiving statin therapy, 1% (n=13) would now qualify due to CHD, 5% (n=52) due to diabetes, 0.3% (n=3) due to CHD and diabetes mellitus (n=3) and 1% (n=9) due to prior ischemic stroke. 5% (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% (Framingham-CHD risk equations), and would therefore 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%. Considering the whole GCKD cohort, implementing the recommendations of the new guideline would increase statin prescription rate from 47% to 88%.

Age group	Previous practice		Application of new guideline	
	With statin	Without statin	Additional condition required	Newly eligible for statin
≥ 50 yrs N=4224 (81% of GCKD cohort)	2196	2028	*Not applicable*	2028
18-49 yrs 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)

The assumption that many CKD patients ≥ 50 years of age will have an estimated 10-year risk for CHD of >10% played an important role in the development of the novel KDIGO guideline. Therefore, we analyzed the distribution of risk in that age group in patients not treated with a statin. Using the Framingham-CHD risk equations, **68% of patients ≥ 50 years of age currently not on a statin had an estimated 10-year risk of CHD of >10%**. In addition, we also calculated atherosclerotic events risk according to the new 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% an atherosclerotic event risk of >7.5%**, which is the threshold for statin therapy recommended by the new ACC-AHA guidelines. In addition, 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 below**).

	10-year risk for atherosclerotic CV event (ACC-AHA Pooled Risk Equations)							
Parameter	≤ 5% N=122	>5-≤7.5% N=106	>7.5-≤10% N=98	>10-≤12.5% N=132	>12.5-≤15% N=126	>5-≤7.5% N=116	>17.5-≤ 20% N=128	> 20% N=1001
Age (median, IQR) - yr	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/m²	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)
Coronary heart disease – n (%)	5 (4)	3 (3)	6 (6)	9 (7)	8 (6)	6 (5)	8 (6)	151 (15)
Cerebrovascular Disease – n (%)	1 (1)	2 (2)	8 (8)	8 (6)	6 (5)	6 (5)	7 (5)	80 (8)
Peripheral Vascular Disease – n (%)	2 (2)	2 (2)	4 (4)	5 (4)	10 (8)	7 (6)	8 (6)	94 (9)
Any of these 3 conditions – 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/1.73m²	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 creatinin 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

Values are mean ± SD unless indicated otherwise

Conclusions

In the GCKD study cohort, slightly less than half of patients (47%) were found to be on statin therapy at baseline. Apparently, established atherosclerotic CV disease was the main driver for the decision to prescribe statin treatment before publication of the novel KDIGO guideline. Full implementation of the KDIGO guideline would almost double the number of patients with statin prescriptions from 47% to 88%. Based on prevalent co-morbidities and risk estimates, the universal recommendation for statin use in CKD patients ≥ 50 yrs appears justifiable.

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