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Treating chronic kidney disease in Danish primary care: results from the observational ATLAS study

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Abstract

Objectives To describe the clinical characteristics, comorbidity, and medical treatment in a primary care population with chronic kidney disease (CKD). Additionally, to investigate how primary care physicians (PCPs) diagnose, manage and treat impaired kidney function, including uptake of cardio-renoprotective renin–angiotensin–aldosterone system inhibitors (RAASis) and sodium glucose co-transporter 2 inhibitors (SGLT2is).

Design An observational study of CKD prevalence, treatment patterns and comorbidities in primary care based on patient record data combined with a questionnaire on diagnosis, management and treatment of impaired kidney function in a real-world, primary care setting.

Setting In all 128 primary care clinics in Denmark of 211 randomly invited and a quetionnaire completed by 125/128 participating PCPs.

Methods A computerized selection identified 12 random individuals with CKD per clinic with ≥ 2 measurements of eGFR < 60 mL/min/1.73 m^2 or UACR > 30 mg/g within two years (*N* = 1 497). Pre-specified data collected from individual electronic health records included demographics, clinical variables, comorbidities, and relevant prescribed medications.

Results Of the CKD study population (*N* = 1 497), 80% had hypertension, 32% diabetes (DM), 13% heart failure (HF), 59% no DM/HF. ACEis/ARBs were prescribed to 65%, statins to 56%, SGTL2is to 14%, and MRAs to 8% of all individuals. Treatment patterns differed between individuals with varying comorbidities, e.g., ACEis/ARBs usage was higher in DM (76%) or HF (74%) vs. no DM/HF (58%), as was statin usage (76% in DM vs. 45% in no DM/HF). SGTL2i usage in no DM/HF was low. Most PCPs identified CKD using eGFR < 60 mL/min/1.73 m^2 (62%) or UACR > 30 mg/g (58%) and 62% reported initiating treatment to retard kidney function decline.

Conclusions Despite good PCP awareness and wish to use relevant guidelines, a gap exists in implementation of cardio-renoprotective treatment, especially in individuals without DM/HF. This offers an opportunity for clear recommendations to PCPs to optimize early cardio-renal protection in individuals with CKD.

Keywords Chronic kidney disease, Primary care, Treatment, Cardio-renal protection, Nephrology, Observational study, Questionnaire, Real-world data

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Strengths and limitation of this study

- This was a large, observational study on the current diagnosis and treatment patterns of individuals with early chronic kidney disease (CKD) by primary care physicians (PCPs) in 125 primary care clinics in Denmark, and described their awareness, perception and adoption of cardio-renoprotective agents.
- Unique patient-record data and PCP responses to a questionnaire were used to provide important information on current clinical practice in CKD in the primary care setting.
- CKD was classified based on ≥ 2 measurements of estimated glomerular filtration (eGFR) < 60 mL/min/1.73 m^2 and/or urine albumin-creatinine ratio (UACR) > 30 mg/g over the last 2 years.
- There was a limited selection of PCPs/primary care clinics (a sample size of approximately 7.5% of Danish general practice). High PCP participation and study completion ensured minimal selection bias.
- The voluntary nature of PCP study participation (accepting an invitation to participate) may have generated bias towards those with an interest in CKD, and may not reflect the general patient population or all clinical practice in Denmark.

Introduction

Chronic kidney disease (CKD) is prevalent in over 850 million people worldwide [1]. Despite few and silent early-stage symptoms, CKD is associated with an increased risk for the development of end-stage kidney disease (ESKD), cardiovascular disease (CVD), premature mortality, and an overall significant burden of disease and healthcare costs [1–5]. Risk factors for the development of CKD are multifactorial [2] and the large population of individuals with CKD would likely benefit from early diagnosis, risk assessment, and effective treatment [1, 4, 5]. Elevated urinary albumin excretion, measured by urine albumin-creatinine ratio (UACR), and reduced glomerular filtration rate (GFR), based on estimated glomerular filtration rate (eGFR), are both markers of end-organ damage and increased CVD risk and mortality [6, 7].

As kidney function declines, the risk for stroke, myocardial infarction, heart failure (HF), peripheral artery disease and all-cause and cardiovascular mortality increases, and is already evident at early stages of increased albuminuria and/or reduced kidney function (GFR < 60 mL/min) [7–10] Typically, individuals with CKD are (only) referred to nephrology specialists for the treatment of secondary complications and preparation for renal replacement therapy at an advanced disease stage, when eGFR has fallen below 30 mL/min/1.73 m^2 [11]. Thus, to prevent progression to ESKD and premature CVD, CKD must primarily be identified and treated in primary care, [4, 12, 13] where early diagnosis and treatment of CKD are vital and supported by international [4, 14, 15] and national [16, 17] guidelines.

Antihypertensive treatment, particularly the renin–angiotensin–aldosterone system inhibitors (RAASis) angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) and, in diabetic nephropathy, mineralocorticoid receptor antagonists (MRAs), delay the progression of CKD to ESKD [15, 18–25]. Moreover, they are guideline recommended, as are interventions to control metabolic parameters, such as hyperglycaemia and dyslipidaemia [4, 14, 15]. Additionally, sodium glucose co-transporter 2 inhibitors (SGLT2is) have proven effective in reducing CKD progression and the risk of ESKD, CVD, and premature death when co-administered with RAASis [26, 27] hence, they are now also being incorporated into updated guidelines [14, 17, 28].

Little is known about the clinical characteristics and medical treatment of individuals with CKD in primary care clinics, including the uptake of cardio-renoprotective treatments like RAASis and SGLT2is by PCPs. Therefore, the objectives of this study were to describe the primary care population with decreased eGFR and albuminuria at risk of developing more severe CKD and premature CVD, and to examine the awareness and habits of PCPs in regard to CKD and treatment patterns, particularly cardio-renoprotective agents, in this at-risk patient population.

Methods

Study setting

This observational study was conducted at primary care clinics throughout Denmark between February 6th and June 7th 2023 (the data collection period). PCPs representing 211 primary care clinics across all geographical regions of Denmark were informed of the ATLAS study by distribution of written and online information about the project with an opportunity to enrol, as described previously [29].

Study populations

Retrospective analysis on CKD treatment patterns in primary care. Data were collected at each participating clinic under guidance from a study representative to ensure a uniform approach across all participating primary care clinics. A standardized (retrospective) search of electronic patient journals was performed by the PCP at their clinic to identify and randomly select individuals with signs of impaired kidney function and thus currently

assigned to their clinic. Individuals with a minimum of one eGFR value < 60 mL/min/1.73 m^2 and/or a measurement of UACR > 30 mg/g within the last five years were identified. Subsequently, a computerized selection process (blinded to both study representatives and PCPs) identified a maximum of 12 randomly selected patients per clinic who did not fulfil the pre-specified exclusion criteria. The latter comprised patients who: were not assigned to the clinic (deceased, moved location or not registered as a patient at the clinic); were aged < 18 years; were in dialysis treatment or had had a kidney transplant; were assigned to a reduced level of treatment or clinical management (i.e., individuals who were terminally ill and/or frail elderly and/or nursing home residents); and, did not have two measurements of either eGFR < 60 mL/min/1.73 m^2 or UACR > 30 mg/g within the last two years [30].

For patients included in the final study population, pre-specified data based on a thorough review of each patient's electronic health journal were communicated orally by the PCP to the study representative. Data included: Age, sex, hight, weight, BMI, smoking status, blood pressure, peripheral oedema, AND comorbidities: CKD, Type 2 diabetes, ischemic heart disease, congestive heart failure, urine tract obstruction, systemic rheumatic disease, hypertension, active cancer disease, AND relevant prescribed medications: ACEi, ARB, Loop-diuretics, thiazide, mineralocorticoid receptor blockade, SGLT2-i, NSAID, oral anti coagulation.. Patient with type 1 or type 2 diabetes were analyses as having diabetes as these patient patients with type 1 diabetes usually attend primarily are cared for in outpatients clinics at a hospital setting and not routinely in primary physician care. These were recorded in the study database by each study representative to ensure patient anonymity for everyone but the PCP. All data were anonymized and stored securely in the study database.

The study was conducted according to the Declaration of Helsinki, and in full compliance with Danish law.

PCP perspective on CKD questionnaire

Following invitation acceptance and as part of the data collection process, each participating PCP was asked to complete a questionnaire in parallel to participating in the main retrospective analysis. The questionnaire focused on how the PCP diagnosed, managed and treated individuals with albuminuria and comprised 19 questions most of which were multiple-option questions with some open-ended questions and the option to add free text comments (see Supplemental Material). All responses were entered directly into the study database by the study representative to provide additional data for a more comprehensive perspective on the current treatment of individuals with early CKD in the nationwide primary care setting.

Data analysis

For the retrospective analysis, normally distributed data are presented as n (%) ± standard deviation (SD), whereas non-normally distributed data are presented as median values with interquartile ranges (IQR). PCP responses to the questionnaire are presented as the number and percentage of respondees, and examples of responses that further elaborate on the findings are presented as citations.

Results

Overall PCP/primary care clinic participation

Of the 211 invited PCPs, 83 declined the invitation to participate, and 128 accepted; of these, 125 completed the study and questionnaire, representing 125 clinics (Fig. 1).

Current CKD treatment patterns in primary care: study population

In the 125 participating primary care clinics covering 445 882 citizens across Denmark, a total of 38 878 (12%) individuals had impaired kidney function (eGFR < 60 mL/min/1.73 m^2) and/or elevated albuminuria (UACR > 30 mg/g). Subsequently, 3 992 were randomly selected and their medical records were audited for exclusion criteria. Individuals without measurement of either eGFR or UACR within 24 mounts were excluded. The final study population comprised $N = 1\ 497$ individuals with CKD (Fig. 1).

Description of the study population

The population was elderly with a mean age of 77 years and an equal distribution of males and females. On average, eGFR was only mildly reduced (median value 53 mL/min/1.73 m^2 [IQR: 44 to 61]); similarly, median UACR was only slightly elevated (33 mg/g [IQR: 11 to 85]). Over two thirds of individuals (73%) had a reduced eGFR (< 60 mL/min/1.73 m^2), whereas 37% ($n = 555$) had elevated UACR (> 30 mg/g) and 31% ($n = 467$) had missing information on UACR. The mean haemoglobin value for the study population was 8 mmol/L and HbAa1c was > 48 mmol/mol in 19% of individuals. The mean total cholesterol level was 4.5 mmol/L, and 35% had LDL levels > 2.5 mmol/L. Potassium levels were > 4.5 mmol/L in 13% of individuals (Table 1).

The distribution of the 1 029 individuals from the study cohort with both eGFR and UACR measurements is shown in the heat map (Fig. 2), based on the KDIGO CKD criteria risk categories, [30] where values of eGFR and UACR are used to classify risk of CKD progression.

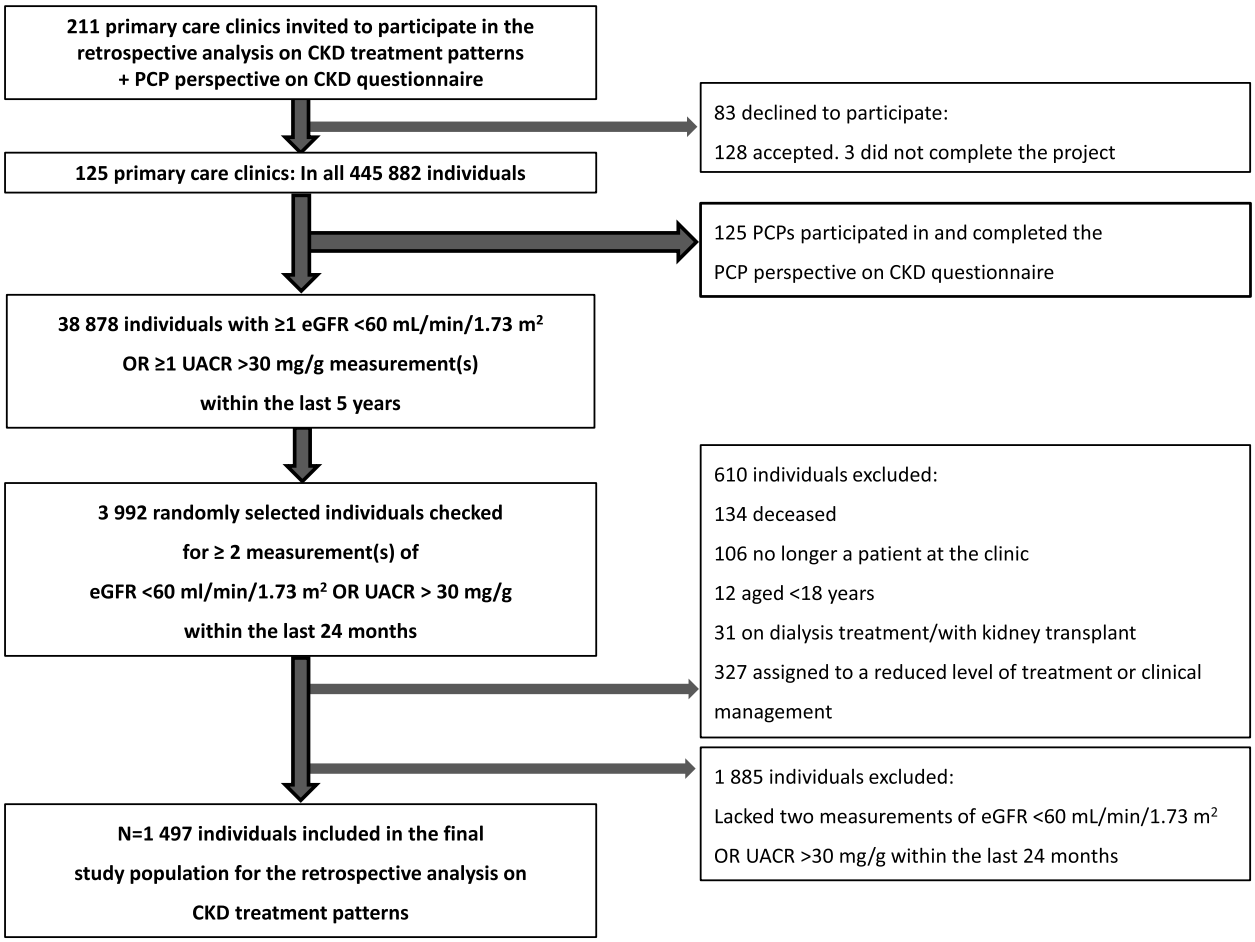

Fig. 1 Patient flow and study population selection. CKD, chronic kidney disease, eGFR, estimated glomerular rate; UACR, urine albumin/creatinine ratio

The majority of individuals were at moderate risk of CKD progression and increased risk of CVD (50%), with few at low risk (9.1%). In contrast, almost half of the population were at high (24%) or very high (17%) risk. A total of 475 individuals had UACR levels of < 30 mg/g, whereas the majority ($n=428$) had eGFR levels of 45 to 60 mL/min/1.73 m^2. Thus, the heat map confirms that a substantial proportion of individuals in this primary care population had a clearly increased risk profile based on these two parameters.

Treatment patterns in the study population

Current medication(s) prescribed to individuals in the study population, divided according to comorbidities are summarized in Table 2. Overall, 80% had hypertension, 32% had diabetes and 13% had HF, while 59% did not have either DM or HF. Median eGFR levels ranged from 48 to 53 mL/min/1.73 m^2 regardless of comorbidity, whereas the highest levels of albuminuria were present in individuals with DM (median 46 mg/g) or with hypertension (median 36 mg/g).

Overall, ACEis or ARBs were prescribed to 65% of all individuals, statins to 56%, SGTL2is to 14%, while glucagon-like peptide-1 receptor agonists (8%) and MRAs (8%) were the least prescribed medications.

While the number of individuals with DM or HF ($n=673$, 45%) was similar to those with neither of these comorbidities ($n=888$, 59%), the treatment patterns based on prescribed medication(s) differed substantially. For example, ACEis or ARBs were more commonly prescribed to individuals with DM (76%) or HF (74%) than to those with no DM or HF (58%). A similar prescription pattern was seen with loop-diuretics and MRAs. Although SGLT2is were prescribed to around one third of individuals with DM (38%) or HF (28%), they were rarely prescribed to individuals with only CKD, i.e. with neither DM nor HF (1%).

For a clinically relevant classification, data were further stratified by eGFR and UACR or a combination

Table 1 Description of the study population, $N = 1\,497$

Variable	Category	Value
Age, years		77 (11)
Gender[a], female		751 (50)
Smoking status[a]	Daily	198 (13)
	Occasionally	14 (0.9)
	Stopped	492 (33)
	Never	522 (35)
	Unknown	271 (18)
eGFR, mL/min/1.73 m^2, median (IQR)		53 (44–61)
eGFR[a]	> 90 mL/min/1.73 m^2	107 (7.1)
	60–90 mL/min/1.73 m^2	304 (20)
	30–60 mL/min/1.73 m^2	998 (67)
	< 30 mL/min/1.73 m^2	88 (5.9)
UACR, mg/g, median (IQR)		33 (11–85)
UACR[a]	< 30 mg/g	475 (32)
	30–300 mg/g	458 (31)
	> 300 mg/g	97 (6.5)
	Missing	467 (31)
Haemoglobin, mmol		8.4 (1.0)
HbA1c, mmol/mol		44 (1.1)
HbA1c[a]	> 48 mmol/mol	291 (19)
Total cholesterol, mmol		4.5 (1.1)
LDL, mmol		2.3 (1.0)
LDL[a]	> 2.5 mmol/L	523 (35)
Potassium[a]	> 4.5 mmol/L	196 (13)

All values are mean (SD) if not shown as median (IQR). [a]Categorical values are shown as n (%)

eGFR estimated glomerular rate, *LDL* low-density lipoproteins, *IQR* interquartile range, *SD* standard deviation, *UACR* urine albumin/creatinine ratio

in individuals with DM or HF and those with no such comorbidity, as shown in Fig. 3. For all strata displayed in Fig. 3 (panels A to D) based on eGFR with or without inclusion of the UACR level, the usage of ACEis or ARBs, SGLT2is and statins was higher in individuals with DM or HF comorbidity compared to those with no DM or HF. Only in the strata with eGFR < 60 mL/min/1.73 m^2 and UACR > 300 mg/g was ACEi or ARB usage similar (77%) in these two categories; however, usage of SGLT2is or statins remained lower in individuals with no DM or HF compared to those with DM or HF (25% vs. 42%, respectively, for SGLT2is and 65% vs. 77%, respectively, for statins) (Fig. 3, panel D).

PCP perspective on CKD: diagnosis and treatment in the primary care setting

The questionnaire and qualitative data from interviews with PCPs ($N = 125$) are presented in the Supplemental Material, with "Q" here referring to specific questions/responses. In summary, most PCPs were aware of and used CKD guidelines, including local guidelines (most commonly diabetes guidelines) to diagnose (68%; 85/125) (Q6) and treat (70%; 88/125) (Q12) their patients. Seventy percent (88/125) of PCPs stated that local kidney disease guidelines should be prioritized (Q2). PCPs reported to a high degree using eGFR < 60 mL/min/1.73 m^2 (62%; 77/124) or UACR > 30 mg/g (58%; 64/111) to identify individuals with CKD (Q3). Of 119 PCPs who used eGFR measurements to diagnose CKD, 53 (45%) used a persistent eGFR of < 60 mL/min/1.73 m^2. Of those who used UACR ($n = 106$), 55 (52%) used a persistent UACR of > 300 mg/g, and 45 (43%) used 30 mg/g (Q4).

Thirty-eight percent (48/125) of PCPs often spoke to patients with an eGFR < 60 mL/min/1.73 m^2 as having CKD, whilst 38% (47/125) reported rarely doing so and 19% (23/125) never did so (Q10). They reported discussing CKD with their patients when eGFR fell below 45 mL/min/1.73 m^2 (49%; 61/125) and when eGFR was < 60 mL/min/1.73 m^2 (32%; 40/125) (Q11). In the free text, two PCPs stated that it depended on their patients' "age and entire medical history/comorbidity".

CKD classification based on last eGFR and UACR				Urine albumin to creatinine ratio categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30–300 mg/g	>300 mg/g
eGFR categories (mL/min/1.73 m²)	G1	Normal or high	>90	1.1	7.9	1.0
	G2	Mildly decreased	60–90	8.0	14.7	2.7
	G3a	Mildly to moderately decreased	45–60	27.1	12.3	2.1
	G3b	Moderate to severely decreased	30–45	8.0	7.4	2.4
	G4	Severely decreased	15–30	2.0	2.0	1.1
	G5	Kidney failure	<15	0	0.1	0.1

Fig. 2 Distribution of baseline kidney function and risk of progression of CKD based on overall kidney function (eGFR) and urine albumin-creatinine ratio levels in the 1 029 subjects with measurement of both eGFR and UACR. The percentage of patients with both eGFR and UACR measurements. Risk of CKD progression indicated by colour: green = low risk; yellow = moderate risk; orange = high risk; light red and red = very high risk. Reproduced with inspiration from de Boer, et al. [31] CKD, chronic kidney disease; eGFR, estimated glomerular rate; UACR, urine albumin-creatinine ratio

Table 2 Patient characteristics and prescribed medication(s), by diagnosis

Diagnosis categories, n (%)		All 1 497 (100)	Diabetes 481 (32)	Heart failure 192 (13)	Hypertension 1 191 (80)	No diabetes or heart failure 888 (59)
Age, years, mean (SD)		77 (11)	75 (10)	80 (10)	77 (10)	77 (11)
eGFR, ml/min/1.73 m^2, median (IQR)		53 (44–61)	53 (42–71)	48 (38–57)	53 (44–62)	53 (46–60)
UACR, mg/g, median (IQR)		33 (11–85)	46 (18–116)	22 (9–79)	36 (11–88)	27 (9–74)
UACR, n (%)	0–30 mg/g	475 (32)	143 (30)	58 (30)	384 (32)	296 (33)
	30–300 mg/g	458 (31)	197 (41)	39 (20)	402 (34)	237 (27)
	> 300 mg/g	97 (7)	44 (9)	8 (4)	81 (7)	50 (6)
	Missing	467 (31)	97 (20)	87 (45)	324 (27)	305 (34)
ACEi/ARB		973 (65)	364 (76)	142 (74)	901 (76)	518 (58)
Beta-blocker		562 (38)	202 (42)	129 (67)	479 (40)	274 (31)
CCB		565 (38)	197 (41)	46 (24)	534 (45)	341 (38)
Loop-diuretic		393 (26)	153 (32)	130 (68)	324 (27)	157 (18)
Thiazide		350 (23)	122 (25)	14 (7)	334 (28)	218 (25)
MRA		124 (8)	52 (11)	53 (28)	105 (9)	39 (4)
SGLT2i		215 (14)	182 (38)	54 (28)	180 (15)	12 (1)
GLP-1 RA		119 (8)	107 (22)	22 (12)	102 (9)	9 (1)
Statin		845 (56)	367 (76)	125 (65)	708 (59)	402 (45)
NSAID		84 (6)	25 (5)	10 (5)	66 (6)	53 (6)
OAC		786 (53)	268 (56)	153 (80)	640 (54)	415 (47)

Categorical values are shown as n (%) if not shown as mean (SD) or median (IQR interquartile range). Diabetes is the combination of either type 1 or type 2 diabetes

ACEi angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *HF* heart failure, *DM* diabetes mellitus (includes type 1 and type 2), *eGFR* estimated glomerular rate, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *IQR* interquartile range, *MRA* mineralocorticoid antagonist, *NSAID* non-steroidal anti-inflammatory drug, *OAC* oral anticoagulant, *SGLT2i* sodium glucose co-transporter 2 inhibitor, *UACR* urine albumin/creatinine ratio

Sixty-two percent (78/125) of PCPs reported initiating treatment to retard kidney function decline when eGFR fell below 60 mL/min/1.73 m^2 and UACR exceeded 30 mg/g with 68% (85/125), with PCPs treating underlying symptoms "as well as they can" (Q13). Additional comments indicated that PCPs initiated treatment depending on the "clinical picture (comorbidity profile), blood tests and UACR in combination" or when eGFR levels dropped below 45, 35, 30 or 25 mL/min/1.73 m^2. Most PCPs 87% (109/125) initiated ACEi/ARB treatment for CKD followed by SGLT2is (52%; 65/125) and 10% (13/125) treated with statins. Diuretics were the most commonly used third-line option overall (33%; 41/215) (Q15).

Most commonly, PCPs reported using the following triggers to refer a patient to the nephrology department (Q17): eGFR (104/125), UACR (87/125), a background of hypertension (87/125), and persistent albuminuria (70/125). Of the 104 PCPs who referred due to eGFR, 76% ($n=79$) reported using an eGFR measurement of < 30 mL/min/1.73 m^2, while around half of the 87 who referred due to UACR reported using a UACR measurement of > 700 mg/g ($n=43$; 49%) or UACR > 300 mg/g ($n=39$; 45%).

Discussion

The ATLAS study provides a unique and comprehensive overview of current medical treatment in a large, randomly selected sample of individuals with CKD followed in Danish primary care by voluntarily participating PCPs. The study population comprised almost 1 500 individuals with CKD of whom over 40% with both eGFR and UACR measurements ($n=1\,029$) were classifiable as high risk by the KDIGO heat map criteria, and 50% were at moderate risk (≥ 60 mL/min/1.73 m^2 and UACR 30–300 mg/g). Since individuals with CKD stage 3 (eGFR 30–60 mL/min/1.73 m^2) are already at a considerably elevated risk of CVD and ESKD, [5, 8] with risk of early mortality increasing continuously as kidney function decreases, early and aggressive pharmacological cardio-renoprotective treatment in these individuals is pivotal [3, 4, 32]. However, most individuals with CKD in this study did not yet receive comprehensive cardio-renoprotective treatment, particularly those with no DM or HF.

In this observational study in Danish primary care, a rather large proportion of individuals with CKD without DM or HF received ACEis/ARBs (58%) or statins (45%) yet only a minority were treated with SGLT2is. This suggests that treatment with SGLT2is for the specific

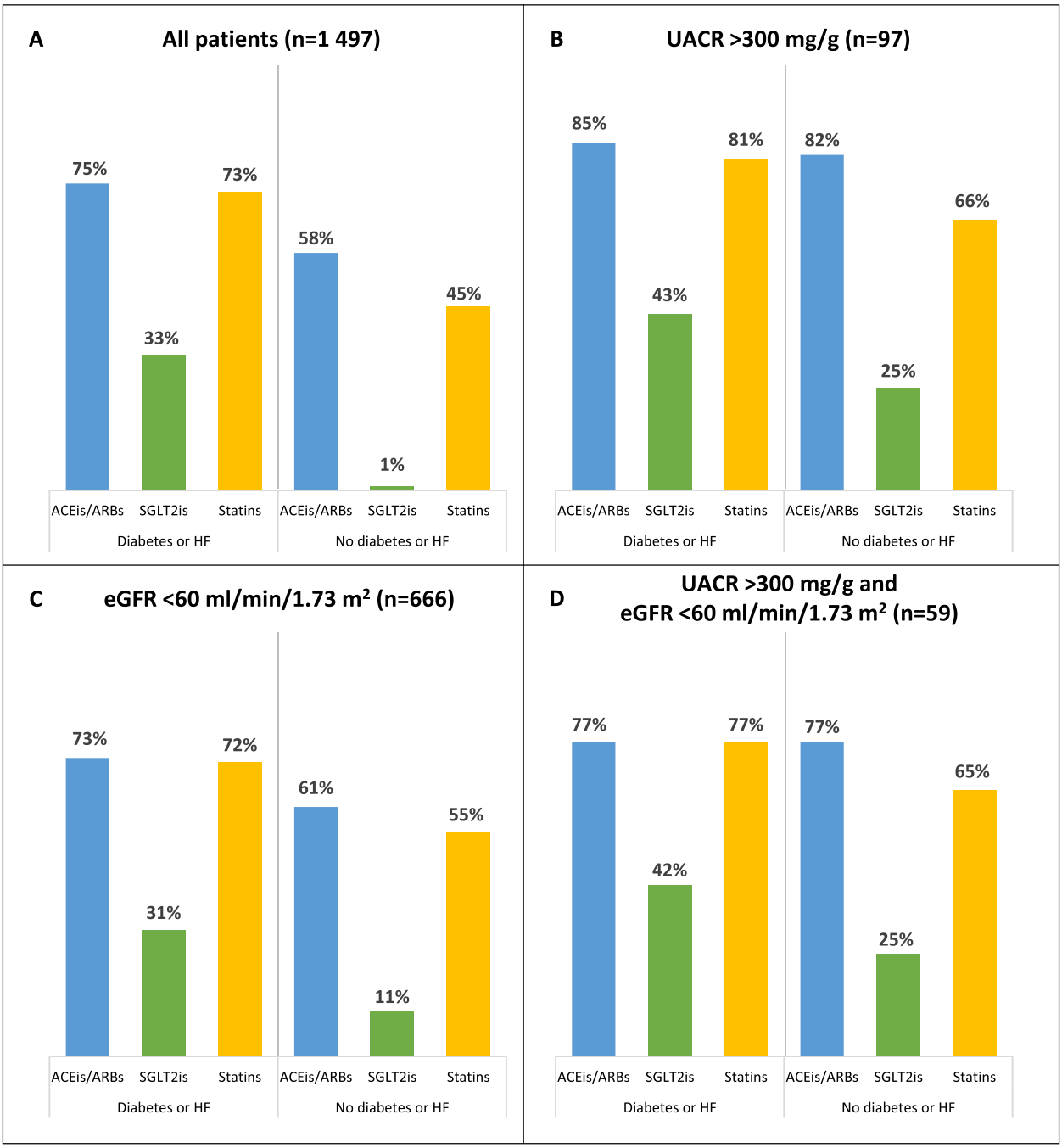

Fig. 3 Use of kidney-relevant treatment (percentage of prescribed medications) in individuals with diabetes (type 1 or type 2) or heart failure compared to individuals without these comorbidities, by subgroups of UACR, eGFR or a combination of eGFR and UACR categories**.** Each subgroup was stratified by comorbidity, specifically individuals with DM or HF and those with no DM or HF. Usage of ACEis/ARBs, SGLT2is and statins was compared between the two strata in (**A**) the total study population; **B** individuals with a last UACR measurement of > 300 mg/g; **C** individuals with a last eGFR measurement of < 60 mL/min/1.73 m^2; and, **D** individuals with last measurements of eGFR < 60 mL/min/1.73 m^2 *and* UACR > 300 mg/g. ACEis, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers; DM, diabetes mellitus (type 1 or 2); eGFR, estimated glomerular rate; HF, heart failure; SGLT2is, sodium glucose co-transporter 2 inhibitors; UACR, urine albumin/creatinine ratio

indication of CKD is still in early implementation in primary care in Denmark compared to older, well-known agents with cardio-renal benefits in this population. Conversely, we found that the majority of individuals with CKD *and* DM/HF comorbidities received ACEis/ARBs (75%) and statins (73%) and one third (33%) received SGLT2is. Thus, while PCPs are familiar with SGLT2is, this suggests that SGLT2is are primarily prescribed for these comorbidities rather than for CKD per se in this real-world, primary care setting, although the Danish Nephrology Sociathy published guide-line on use of SGLT2is in March 2021.

In Denmark, individuals with DM and/or HF are seen regularly by PCPs, representing an opportunity to screen and monitor for CKD. Individuals with DM, and often those with hypertension and HF, undergo systematic, annual check-ups based on clear treatment algorithms. However, the current, less systematic screening and monitoring for non-diabetic CKD may be comparable to that of DM 20 years ago [5, 13, 33, 34]. Hence, applying the same systematic screening as in individuals with DM to non-diabetic populations could offer a paradigm shift for the identification, diagnosis and monitoring of CKD.

Our questionnaire confirmed that most PCPs were aware of and could identify and diagnose CKD. This is important since early CKD diagnosis is reported as fundamental to improving patient outcomes and reducing healthcare costs [3, 4, 33] supported by multifactorial treatment [32, 35]. CKD is diagnosed and staged using eGFR and UACR measurements. UACR testing is a universal challenge, although systematic control as implemented in DM seems to improve completion [13]. In the primary care setting beyond Denmark, UACR testing rates for type 2 DM (T2DM) are known to have been suboptimal [36, 37] and CKD is significantly underdiagnosed [5, 33, 37]. Unlike other chronic diseases with established strategies for screening, there has been no consensus in regard to early identification and intervention for CKD. Several studies have estimated the feasibility and cost vs. benefit of general screening for CKD, however the implementation screening is still debated [38, 39]. Guidelines on evaluating and managing early CKD in high risk individuals are available but have not been universally adopted [4]. This is unfortunate as risk stratification and treatment of high-risk individuals seem to be cost-effective [4, 40, 41]. Including UACR in the CKD diagnostic and monitoring toolkit can improve CKD detection by albuminuria levels and offers PCPs an opportunity to reduce CKD progression and prevent premature CVD [40, 42]. Here, PCPs reported using UACR to diagnose CKD, and despite enrichment of the study population for UACR, the large proportion of individuals with both eGFR and UACR measurements indicates that PCPs are including UACR in their diagnostic work-up of CKD in Danish primary care, even though the threshold for diagnosis varies.

PCPs have a broad, multidisciplinary remit with great demands on their time, and require clear and current treatment guidelines [43]. A lack of awareness of CKD guidelines as regards diagnosing CKD and clarity as to who to prescribe which treatment to and when may have influenced the readiness of PCPs to prescribe SGLT2is, especially for individuals with CKD without DM or HF, resulting in clinical inertia. Originally prescribed for T2DM, SGLT2is were discouraged in individuals with impaired kidney function because of poor blood glucose-lowering effects in these subjects. This may still influence SGLT2i implementation for individuals with CKD, even though several studies have since demonstrated both cardio- and reno-protective effects of SGLT2is in individuals both with and without DM [26, 27, 44, 45]. On this background, SGLTis are now being recommended for individuals with eGFR 20–90 mL/min/1.73 m^2 and UACR > 200 mg/g or eGFR 20–45 mL/min/1.73 m^2 regardless of albuminuria in combination with ACEis/ARBs and statins [14, 17]. Guidelines attempt to address this by clarifying the high risk of individuals with CKD, and may help to resolve any residual doubt about treatment in primary care. However, it is pivotal for implementation that guidelines are effectively disseminated throughout primary care to aid PCPs.

Additionally, because our study population was elderly (mean age 77 years), PCPs may have refrained from prescribing SGLT2is due to a natural belief that they could be associated with an increased risk of adverse events (e.g., hypotension, dehydration, and infections) in this population. However, a considerable number of elderly patients have been included in cardiovascular outcome trials over the last decade, and there is now good evidence that SGLT2i treatment is safe even in elderly and frail patients, [46, 47] with a similar low risk of adverse events as in younger patients. Moreover, there is no age modification of the cardiovascular and renal risk reductions in the cardiovascular outcome trials, indicating a similar relative risk reduction over age strata, and a likely reduction in the number needed to treat in the elderly due to a larger absolute risk of cardio-renal disease development [47, 48]. Thus, even in the present elderly population, SGLT2is should be considered safe and associated with a markedly reduced risk of severe cardiac and renal events, particularly because frailer patients with a reduced treatment level ambition were deliberately excluded from the study.

Most PCPs in the ATLAS study reported being aware of and using CKD guidelines to diagnose and treat CKD. Yet treatment patterns may have been influenced by

the criteria they used to initiate treatment. Two thirds of PCPs sought to retard kidney function decline when eGFR fell below 60 mL/min/1.73 m^2 and UACR exceeded 30 mg/g, as was supported by ACEi/ARB and statin treatment patterns in the DM or HF group, but less so in the no DM or HF group. Other PCPs reported initiating treatment when eGFR levels dropped below 45 mL/min/1.73 m^2 or less; this may be a late stage to initiate cardio-renal protection and suggests that an eGFR < 60 of mL/min/1.73 m^2 as a definitive diagnostic marker for CKD may still be under debate amongst PCPs. This is supported by the fact that a large group of PCPs only discussed CKD with their patients when their eGFR had fallen below 45 mL/ml/1.73 m^2, sometimes even depending on the "age and comorbidity of patients" (see Supplemental Material).

Encouragingly, almost 70% of PCPs stated that they treated the underlying cause of CKD as well as they could and most did initiate treatment. PCP awareness of cardio-renoprotective benefits of ACEis and ARBs was very good with 86% reporting using ACEis/ARBs first line. While their awareness of SGLT2i cardio-renoprotective benefits was good and 53% of PCPs reported using SGLT2is as second-line treatment for CKD, this did not translate into current prescribing patterns. The addition of SGLT2is to ACEis/ARBs should be considered in all individuals with CKD; yet even the well-established, cardio-renoprotective ACEis/ARBs were used in only 58% of individuals with CKD and no DM/HF in this study. This is an improvement over time compared to similar data from a Danish primary care cohort between 2000 and 2015 [49]. In contrast, ACEi/ARB and statin usage reflected guideline recommendations, and was very good in most individuals with DM or HF (75% and 73%, respectively). MRA usage was relatively low despite guideline recommendations and strong evidence for lowering the risk of all-cause readmission for HF, [50] and use in DM will undoubtedly increase as they are currently added to guidelines for cardio-renal protection [18, 51].

Overall, this study highlights a need for focus on the implementation of cardio-renoprotective agents for the specific indication of CKD [5, 33]. Our analyses did not reveal why treatment was not initiated or continued, but it is known that several challenges are always at stake regarding clinical inertia or non-adherence [52, 53]—some patients will not tolerate medication or will be challenged socioeconomically. A clinic can have a busy time schedule, or lack patient education material or decision tools. A systematic review from 2020 identified a number of barriers and enablers that PCPs face when identifying and managing CKD, especially lack of time, anxiety about communicating a diagnosis of CKD, and a dissatisfaction with current CKD management guidelines. This emphasises the need for clear guidelines and information for both patients and health providers. Indeed, our questionnaire revealed that 70% of PCPs thought that guidelines on kidney disease from the National Society for General Medicine should be prioritized. Another area to address could be the intent of physicians to discuss kidney disease or impairment with patients to increase their knowledge and adherence. Our questionnaire showed that around half of PCPs only spoke to patients regarding CKD when eGFR was below 45 mL/min/1.73 m^2, a state where the decline in eGFR is ongoing and an elevated risk of CVD is already pronounced.

Strengths and limitations

The ATLAS study uniquely used direct patient journal-based as opposed to registry-based data and provided a good representation of real-life treatment of CKD in the primary care setting in Denmark. Selection bias was minimal due to the limited selection of PCPs/primary care clinics and a large study population with kidney impairment assigned to these care clinics (almost 1,500 individuals). Of the 211 PCPs invited to participate, 128 accepted and 125 completed the project. The General Practitioners' Organisation (PLO) registered 1 675 primary care clinics in Denmark in 2022, [54] so the participating PCP sample represents approximately 7.5% of Danish primary care whose level of participation (61%; 128/211) and study completion rates (97.7% [125/128] completed the project) were high.

Nevertheless, ATLAS was an observational study. Invited clinics may have been biased towards an interest in CKD and since PCP participation was voluntary (by invitation to accept), data may not perfectly represent this patient population or overall clinical practice in Denmark, and thus deviate in translation into the general population. Since patients were stratified for CKD stage based on their last eGFR value recorded during the 2-year period, 9% of the study population had normal values of both eGFR and UACR.

Conclusion

The ATLAS study highlights good PCP awareness and a wish to use relevant guidelines; however, a gap exists in the implementation of cardio-renoprotective treatment, especially in individuals without DM/HF. This offers an opportunity for clear recommendations for PCPs to optimize early pharmacological cardio-renal protection in individuals with CKD and an associated risk of premature CVD. ACEi/ARB and statin usage was good in individuals with DM or HF, but lower in non- DM/HF individuals. Additionally, the new treatment modality, SGLT2i, was prescribed to a minority of individuals without DM or HF compared to one third of those with DM and/or HF. This omits many individuals who qualify for SGLT2is based on

eGFR levels alone, indicating an unutilized potential for further cardio-renal protection in these individuals. ATLAS also highlights that some PCPs are first movers as regards prescribing SGLT2is in CKD, and reveals an opportunity for PCPs to optimize awareness of CKD and early pharmacological cardio-renal protection in individuals with CKD who are at risk of premature CVD. Furthermore, this study represents a real-world baseline from which to re-evaluate the implementation of cardio-renoprotective treatments in this setting in 3–5 years' time, where we believe that Danish PCPs will have implemented cardio-renal protection in individuals with CKD to a much greater extent.

Supplementary Information

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Supplementary Material 1.

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Data sharing statement
The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

STROBE checklist
Submitted for an observation cohort.

Authors' contributions
The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors: ML, MC, TS, RB and SK contributed to developing the study methodology, design of the work, the acquisition, analysing and interpretation the data, as well as writing and editing the manuscript, and approving the final manuscript for publication. ML contributede as first author and both SK and RB contributed equally as senior authors in creating the manuscript. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations.

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Data availability
Data sharing statement The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study (including patient data collection) and the questionnaire represented observational, non-interventional, quality-improvement research with significant societal impact using anonymized data and no patient involvement. Thus, no specific legal approval or informed patient consent in accordance with Danish legislation was required.

Consent for publication
Not required, and not done, in accordance to national regulations.

Competing interests
The authors did not receive payment related to the development of the manuscript. All authors received an honorarium from Boehringer Ingelheim with respect to this study for their role as Steering Committee members. ML: has received speaker and consultancy fees from AstraZeneca, Bayer, Boeringer Ingelheim, Novo Nordisk, GlaxoSmithKline, and is an investigator in clinical studies sponsored by Amgen, Bayer, Boehringer Ingelheim, Janssen, MSD and Novo Nordisk. STK: has received research grants from and lecture fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, MSD, Novo Nordisk, and Sanofi and has served as a consultant for Bayer, Boehringer Ingelheim, MSD, Mundipharma, Novo Nordisk, and Sanofi. TS: none; MC: has received speaker/expert testimony honoraria from Novo Nordisk Denmark, Boehringer Ingelheim Denmark, and Abbott Rapid Diagnostics. RB: has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, and Boehringer Ingelheim, is an investigator in clinical studies sponsored by Boehringer Ingelheim, AstraZeneca, Bayer, and has received unrestricted research grants from Boehringer Ingelheim.

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