Primary Care Diabetes 15 (2021) 1007–1011

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Improving frequency of urinary albumin testing in type 2 diabetes in primary care — An analysis of cross-sectional studies in Denmark

Frederik Persson[a,*], Morten Charles[b,d], Johan Vestergaard Povlsen[c], Søren Tang Knudsen[d]

[a] Steno Diabetes Center Copenhagen, Gentofte, Denmark
[b] Research Unit of General Practice, Aarhus University, Denmark
[c] Dept. Renal Medicine C, Aarhus University Hospital, Aarhus, Denmark
[d] Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Article history:
Received 9 February 2021
Received in revised form 21 June 2021
Accepted 8 July 2021
Available online 17 July 2021

Keywords:
Albuminuria
Diabetic kidney disease
Primary care
Type 2 diabetes

ABSTRACT

Background: To ensure high quality standards in chronic care of type 2 diabetes, it is paramount to ensure regular measurement of clinical risk factors. For prevention of diabetic kidney disease, testing for albuminuria and kidney function is vital. The majority of individuals with type 2 diabetes in Denmark are treated in general practice, and given the recent development of kidney-protective treatments, a renewed focus on renal risk factors is important.
Objective: To assess the frequency of albuminuria and kidney function testing in general practice in Denmark and describe developments over the last decade. The proportion of patients with the recommended annual measurements of albuminuria and kidney function was the primary variable.
Methods: We used data from subjects with type 2 diabetes in three cross-sectional general practice studies from 2009 to 2017.
Results: Data from 5592 individuals were available. Almost all subjects (96–99%) in the studies had annual measurement of kidney function performed. During the combined observation period there was a clear increase in the proportion of subjects that had albuminuria measured, from 57.2% to 68.0% to 82.8%.
Conclusion: The regular assessment of renal risk factors in individuals with type 2 diabetes attending primary care in Denmark has seemingly improved over the last decade. This provides the required base for renal risk assessment and appropriate therapy selection.

1. Introduction

In Denmark, as in many western European countries, the majority of individuals with type 2 diabetes (T2D) are cared for in general practice. Prevention of acute and chronic complications is the main purpose of the treatment of type 2 diabetes. Landmark studies as the Steno 2 study [1–3] demonstrated the importance of addressing all risk factors, to ensure multi-organ protection. Therefore, multifactorial interventions, focusing on other factors than lowering of blood glucose, are essential [4]. For every risk factor to be addressed, there is a corresponding necessary clinical or biochemical measure to be recorded. Smoking status must be inquired, and blood pressure measurement under standardized conditions and HbA_{1c} analysis by validated laboratory methods are cornerstones of risk factor identification and control. The same is the case for the renal and cardiovascular risk factor, microalbuminuria [5], a precursor for diabetic kidney disease [6]. To categorize the individual as having normo- micro- or macroalbuminuria, repetitive measures of urinary albumin creatinine ratio (UACR) are recommended as part of the Danish treatment guidelines for T2D management for general practitioners, preferably in a first morning void or a spot urine sample. As treatment-induced reductions in UACR are important indicators of risk reduction [7], annual sampling is recommended, and this approach also provides information on any progression of kidney disease and cardiovascular risk. In one study a >30% reduction in albuminuria was associated with a 62% reduction in renal risk and a 25% reduction in cardiovascular risk compared with an increase in albuminuria [8].

In parallel, creatinine-based assessment of kidney function, in recent years routinely reported by clinical laboratories as estimated glomerular filtration rate (eGFR), is important to monitor and detect individuals at risk, and also recommended as part of the treat-

* Corresponding author.
E-mail address: frederik.persson@regionh.dk (F. Persson).

https://doi.org/10.1016/j.pcd.2021.07.003

Table 1
Characteristics of the studied population from three studies.

	Knudsen et al. [11] T2D N = 2057	Rungby et al. [12] T2D N = 2003	Lange et al. [13] All (T2D and T2D + COPD) N = 1532 (823 + 709)
General characteristics			
Male sex, no (%)	1208 (58.7)	1309 (65.4)	882 (57.6)
Age, yrs (st)	66.2 (11.6)	72.0 (10.4)	69.4 (10.9)
BMI, kg/m^2 (st)	30.8 (5.8)	30.1 (5.9)	30.4 (6.4)
Current smoking, no (%)	327 (15.9)	353 (17.6)	366 (23.9)
Systolic BP, mmHg	132.6 (14.6)	131.4 (15.3)	132 (13.9)
Diastolic BP, mmHg	78.1 (9.0)	75.7 (9.9)	77 (9.8)
eGFR, ml/min/1.73 m^2			
Mean (st)	NA	68.2 (20.0)	72.5 (19.7)
>90	390 (36.0)	404 (20.9)	392 (25.8)
60–90	493 (45.6)	878 (45.4)	754 (49.7)
30–59	181 (16.7)	585 (30.2)	318 (21.0)
<30	18 (1.7)	69 (3.6)	53 (3.5)
Unknown	975 (47.4)*	67 (3.3)	15 (1.0)
Cholesterol, mmol/l			
Total	4.2 (NA)	4.0 (1.1)	4.1 (1.1)
LDL	2.2 (NA)	2.0 (0.9)	2.0 (13.9)
HbA_{1C}, mmol/mol, av (st)	53.1 (16.6)	52.3 (13.4)	52 (13.0)
Albuminuria class, n (%)			
Normoalbuminuria	894 (76)	917 (67.3)	885 (69.7)
Microalbuminuria	247 (21)	373 (27.4)	318 (25.1)
Macroalbuminuria	35 (3.0)	72 (5.3)	66 (5.2)
Unknown	881 (42,8)	641 (32.0)	263 (17.2)
Duration DM, n (%)			
<5 yrs	596 (29.5)	576 (29.2)	376 (24.7)
5–10 yrs	981 (48.5)	720 (36.5)	616 (40.4)
>10 yrs	446 (22.0)	676 (34.3)	531 (34.9)
Unknown	34 (1.7)	31 (1.5)	9 (0.6)
Glucose-lowering treatment, n (%)			
Nonpharmacological treatment only	226 (11.0)	437 (21.8)	214 (14.0)
Metformin monotherapy	779 (37.9)	714 (35.6)	549 (35.8)
Number of patients on 1 drug treatment	1016 (49.4)	951 (47.5)	707 (46.1)
Number of patients on 2–3 drugs	807 (39.2)	602 (30.1)	583 (38.1)
Number of patients on 4–5 drugs	8 (0.4)	13 (0.6)	28 (1.8)
Treatment of CV disease, n (%)			
ACEI/ARB	1364 (66.3)	1301 (65.0)	942 (61.5)
Antihypertensives	1635 (79.5)	1840 (91.9) 0	1253 (81.8)
Statins	1504 (73.1)	1568 (78.3)	1121 (73.2)
Antiplatelet treatment	961 (46.7)	1003 (50.1)	NA
Anticoagulant/antiplatelet treatment	NA	NA	742 (48.4)
CVD	409 (19.9)	2003 (100.0)	
CVD (incl HF)			515 (33.6)
CVD (excl HF)			478 (31.2)

* P-creatinine values recorded as intervals was available in 97,6% (n = 2008) of patients, while e-GFR values were available for a subgroup (n = 1082).

ment guidelines for T2D management (www.vejledninger.dsam.dk/type2/). In T2D, annual decline in kidney function increases with degree of albuminuria. Reduced kidney function is strongly associated with increased mortality in type 2 diabetes. Thus, the ten-year mortality in T2D patients increases from 4.1% without chronic kidney disease (CKD), to 23.9% with impaired kidney function and to 47% in individuals with both impaired kidney function and albuminuria [9].

Despite similar guidelines across countries, a large variation in the frequency of albuminuria measurement has been observed [10], perhaps because implementation of urine sample collection can be less convenient as compared to blood sampling. In Denmark, a previous study in T2D patients followed in general practice reported a less than optimal annual urinary sampling rate of 57.2%, potentially leading to under-diagnosis and under-treatment of albuminuria [11].

To highlight this issue, we compared data from available cross-sectional reports from on T2D patients followed in the primary care sector in Denmark, to assess and report recent developments. The primary variable of interest was the proportion of subjects in each report with annually measured albuminuria. In addition, we present the proportion of participants with chronic kidney disease (CKD) and levels of eGFR, as presence of CKD increases renal and cardiovascular risk in a general practice population. In addition, the use of modern antidiabetic therapies, i.e., glucagon-like peptide 1 receptor agonist (GLP-1 RA) and sodium glucose co-transporter 2 inhibitors (SGLT2i) is reported.

2. Methods

We used data from three previously conducted cross-sectional studies in general practices in Denmark, published in 2012, 2016 and 2020, respectively. The full details of all three studies have been published previously. The first study had a specific focus on screening for microalbuminuria [11]. A total of 2,057 individuals with type 2 diabetes were randomly selected from 64 general practitioner clinics (GPs) from different geographical areas of Denmark, and electronic medical record data with particular focus on albuminuria and creatinine screening were collated. The second study [12] collected data on prevalence of cardiovascular disease (CVD)

among persons with T2D in general practice. Data on 2,003 patients from 129 GPs were collected, including information on albuminuria and eGFR levels. The third study [13], investigating co-prevalence of T2D and chronic obstructive pulmonary disease (COPD), collected clinical data from 823 patients with T2D and 709 patients with both COPD and T2D from 164 GPs.

Overall, a broad selection of patients and clinic types in relation to geography and demography was ensured.

Data are presented as mean ± standard deviation (SD, normally distributed parameters) or as median (interquartile range (IQR)). We decided not to perform formal statistical analyses on the proportions of albuminuria screened subjects in the three study populations included. This decision was based on the fact that i) the present study was merely descriptive in nature, ii) the two latest samples (2016 and 2020) were collected for different purposes, and iii) the three study populations included were somewhat heterogenous.

The study was approved by The Danish Data Protection Agency, and the participation of the GPs was approved by the Danish Medical Association. Since these were (non-drug) non-interventional studies, approvals from the ethical committee and the Danish Medicines Agency were not mandatory.

3. Results

The clinical and laboratory characteristics of the subjects in the three studies are presented in Table 1. In the third study [13], the fraction of patients unscreened for albuminuria did not differ between the groups with T2D versus T2D and COPD (17.3 vs. 17.1%, respectively). For clarity, it was therefore decided to combine these two groups in the table. During the combined period of data collection (from 2009 to 2017) the proportion of subjects that had albuminuria measured during an observation period of 12 months, increased gradually from 57.2% to 68.0% to 82.8%. In the first study from 2009, there were 3% with macroalbuminuria and 21% with microalbuminuria among the screened subjects. In the two latter studies, these proportions were 3.6% and 4.3% with macroalbuminuria and 18.6% and 20.8% with microalbuminuria, respectively.

Creatinine and eGFR results were more frequently measured as compared to albuminuria, as can be seen in Table 1, with measurements performed for between 96–99% of the study populations. Kidney function was assessed with different level of detail in the three studies. One of the studies, that by design had a 100% prevalence of CVD, reported that 56% of the study population had CKD (eGFR <60 ml/min/1.73 m^2), with no further details. The 2009 study reported 21.5% of the population as having stage 3 CKD (eGFR 30−59 ml/min/1.73 m^2) and 2.5% as having stage 4−5 CKD (eGFR <30 ml/min/1.73 m^2). The most recent study reported stage 3 CKD in 20.8% and stage 4−5 CKD in 4.4% of the study population, respectively.

The two latter studies from 2016 and 2020 reported an increasing frequency of treatment with SGLT2 inhibitors (4.0% and 15.2%, respectively), and GLP-1 receptor agonists (5.4% and 10.1%, respectively).

4. Discussion

We found a marked increase in the proportion of patients with type 2 diabetes in primary care in Denmark with annual albuminuria measurement in three cross-sectional studies spanning 8 years. As screening for albuminuria is a logical prerequisite for risk classification leading to subsequent treatment initiation, this development is comforting. A recent Danish primary care cohort study in patients without cardiovascular disease demonstrated that micro- and macroalbuminuria is associated with higher risk of stroke, myocardial infarction and all-cause mortality, underscoring the continuing importance of albuminuria measurement in primary care [14]. Risk stratification is particularly important when composing a multifactorial treatment intervention strategy as devised from the Steno 2 study, that showed marked cardiorenal benefits of intensive multifactorial intervention against blood pressure, blood glucose, lipids, and hypercoagulation in a study population of high-risk type 2 diabetic individuals with microalbuminuria (1–3).

The demonstration of increased albuminuria measurement frequency in general practice in Denmark over the last decade is even more important, considering the results of recent randomized controlled trials where SGLT2 inhibitors have shown impressive risk reductions of both renal outcomes and hospitalizations for heart failure in high-risk populations [15–17]. Moreover, treatment with GLP-1RA reduce albuminuria levels and in the LEADER trial, liraglutide did even slow the progression to macroalbuminuria, indicating a renoprotective potential [18].

Thus, the benefits of both treatment of established cardiorenal risk factors as well as addition of specific kidney- and cardioprotective antidiabetic agents in persons with type 2 diabetes with elevated albuminuria, regardless of HbA_{1c} levels [4], are well documented, and many other potentially renoprotective agents are being investigated [19]. However, a prerequisite for these cardio-renoprotective interventions is the identification of persons with type 2 diabetes and elevated albuminuria, and since the vast majority of individuals with type 2 diabetes are followed in general practice, regular screening for (micro)albuminuria in the primary care setting is essential.

In Sweden, a country with a similar public primary health care system as in Denmark, measurement of albuminuria in primary care has increased from 68.6% in 2014 to 74.4% in 2019, according to the Swedish National Diabetes Registry (https://www.ndr.nu/#/knappen1, accessed on October 21st 2020). In Norway on the contrary, albuminuria screening in two cross-sectional studies in primary care was low; 37.9% in 2005 and 30.3% in 2014 [20]. Another relevant comparison is the National Diabetes Audit in the UK, reporting a decline in urine albumin measurement from 84.4% of the included population in 2013−14 to 60.8% in 2018−19 (https://files.digital.nhs.uk/B2/24D150/REF161%20National%20Diabetes%20Audit%202018-19%20Full%20Report%201%2C%20Care%20Processes%20and%20Treatment%20Targets.pdf accessed on June 20, 2021).

The reason for the observed increase in the proportion of albuminuria-screened among persons with type 2 diabetes in Danish general practice is probably multifactorial. Since 2011, joint Danish national guidelines (https://vejledninger.dsam.dk/type2/) for the treatment of persons with T2D has been published in a collaboration between the associations of endocrine and general practice doctors, and this approach may facilitate the dissemination of the importance of this screening among GPs in Denmark. Moreover, the high frequency of cardiovascular outcome trials (CVOTs) with positive renal outcomes over the latter years may also have increased the focus on this area. In support of this hypothesis, a recent study suggested that publication of positive CVOTs resulted in an increased prescription of the relevant study drug, shortly after the publication itself [21].

In parallel, and with relevance not only in individuals with type 2 diabetes, an increased focus on CKD in general practice is important, as the conditions has no or only few symptoms. A U.S. mixed-method investigation found “multiple barriers to managing CKD in primary care including at the level of the patient (e.g., low awareness of CKD, poor adherence to treatment), the provider (e.g., staying current with CKD guidelines), and the health care system”, factors that may all lead to difficulty in keeping CKD in focus and achieve a high level of monitoring [22]. Many primary health care

systems now have automated estimation of GFR, and reporting is therefore high and may also have led to increased prescriptions of preventive treatment [23]. Yet, to prevent renal and cardiovascular events it is important not only to measure but also to react to lab reports with eGFR values. In the studies included we found high proportions of eGFR <60 ml/min/1.73 m^2, but we could not assess the clinical consequences or treatments initiated on this basis. The use of guideline-directed treatment with the aim of cardiorenal protection is likely to increase in the future, as has been observed in Scandinavian primary care between 2003 and 2015 [24]. As an example, the standardized implementation and resulting increased use of RAS blocking treatment in T2D may have led to a lower proportion of patients with diabetes and end stage kidney disease in Denmark [25] as compared to USA (www.usrds.org/annual-data-report/).

On a final note, increased attention to the monitoring and treatment of CKD, with or without presence of type 2 diabetes, should also be the focus of primary care, and will likely be included in future national and international guidelines. This is expected following the publication of several studies showing clear renal benefit of SGLT2 inhibition in individuals with chronic kidney disease [17,26–28].

5. Limitations

In this study we had access to three cross-sectional samples to assess our primary variable of interest. Therefore, these data should be regarded as available samples with limits to its representativeness, but as yet there is no national primary care database available in Denmark, i.e., as the CPRD in UK. The first study [11] was initiated with the primary purpose to assess the completeness of screening for microalbuminuria in Danish general practice, whereas data in the other two studies [12,13] were originally obtained for other purposes. However, as shown in Table 1, clinical and laboratory characteristics between samples did not differ as much as could be expected from the selection criteria. Furthermore, in the last study [13], the fraction of patients unscreened for albuminuria did not differ between the groups with and without COPD (17.1 vs. 17.3%, respectively). Moreover, in the 2012 study [11], the frequency of CVD disease did not differ between the patients screened and unscreened for albuminuria (20.2 vs. 19.4%, p = 0.68). Therefore, we chose to include this more selected sample in the article, in order to illustrate the stepwise improvement in screening practice over the study period. Taken together, these observations speak against a major selection bias due to the difference in inclusion criteria between samples.

As clinics were contacted for participation in these studies by Boehringer Ingelheim, clinics with no interaction with pharmaceutical companies were not included, which may limit the representativeness of our data. Similarly, only data from individuals with a certain mobility and level of function could be included, thereby excluding persons in nursing homes etc. However, when comparing characteristics of the participating clinics to the national average regarding size and number of patients at each clinic, our data corresponds well.

6. Conclusion

Albuminuria measurement in subjects with type 2 diabetes in primary care is an important prerequisite for renal risk assessment and proper treatment allocation. The measurement of albuminuria has seemingly improved in primary care in Denmark since 2012, which will provide a solid base for an improved quality of care and prevention of cardiorenal events in the future.

Conflicts of interest

The study was supported by an unrestricted grant from Boehringer Ingelheim. All authors received honorarium from Boehringer Ingelheim in relation to the present study and educational activities.

FP reports having received research grants from AstraZeneca,Novo Nordisk andNovartis and lecture fees from Novartis,Eli Lilly,MSD, AstraZeneca,Sanofi, Novo Nordisk and Boehringer Ingelheim and having served as a consultant for Astra Zeneca, Bayer,Amgen, Novo Nordisk and MSD. MC reports having received lecture fees from Novo Nordisk and Boehringer Ingelheim.

JVP reports having received lecture fees from Baxterand Novo Nordisk and having served as consultant for Boehringer Ingelheim and Mundipharma. STK reports having received research grants from AstraZeneca and lecture fees from Boehringer Ingelheim, MSD, Novo Nordisk, and Sanofi and having served as a consultant for Boehringer Ingelheim, MSD, Mundipharma, Novo Nordisk, and Sanofi.

Acknowledgements

The studies used for this analysis were sponsored by Boehringer Ingelheim Denmark.

References

[1] P. Gaede, H. Lund-Andersen, H.-H. Parving, O. Pedersen, Effect of a multifactorial intervention on mortality in type 2 diabetes, N. Engl. J. Med. 358 (2008) 580–591.
[2] P. Gaede, J. Oellgaard, B. Carstensen, P. Rossing, H. Lund-Andersen, H.H. Parving, O. Pedersen, Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial, Diabetologia 59 (2016) 2298–2307.
[3] J. Oellgaard, P. Gaede, P. Rossing, F. Persson, H.H. Parving, O. Pedersen, Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits, Kidney Int. 91 (2017) 982–988.
[4] J.B. Buse, D.J. Wexler, A. Tsapas, P. Rossing, G. Mingrone, C. Mathieu, D.A. D'Alessio, M.J. Davies, 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (ADA) and the european association for the study of diabetes (EASD), Diabetes Care 43 (2020) 487–493.
[5] H.H. Parving, F. Persson, P. Rossing, Microalbuminuria: a parameter that has changed diabetes care, Diabetes Res. Clin. Pract. 107 (2015) 1–8.
[6] F. Persson, P. Rossing, Diagnosis of diabetic kidney disease: state of the art and future perspective, Kidney Int. Suppl. (2011) 8 (2018) 2–7.
[7] H.J.L. Heerspink, T. Greene, H. Tighiouart, R.T. Gansevoort, J. Coresh, A.L. Simon, T.M. Chan, F.F. Hou, J.B. Lewis, F. Locatelli, M. Praga, F.P. Schena, A.S. Levey, L.A. Inker, C. Chronic Kidney Disease Epidemiology, Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials, Lancet Diabetes Endocrinol. 7 (2019) 128–139.
[8] H.J. Lambers Heerspink, T. Ninomiya, F. Persson, B.M. Brenner, P. Brunel, N. Chaturvedi, A.S. Desai, S.M. Haffner, J.J. McMurray, S.D. Solomon, M.A. Pfeffer, H.H. Parving, D. de Zeeuw, Is a reduction in albuminuria associated with renal and cardiovascular protection? A post-hoc analysis of the ALTITUDE trial, Diabetes Obes. Metab. 18 (2) (2016) 169–177.
[9] M. Afkarian, M.C. Sachs, B. Kestenbaum, I.B. Hirsch, K.R. Tuttle, J. Himmelfarb, I.H. de Boer, Kidney disease and increased mortality risk in type 2 diabetes, J. Am. Soc. Nephrol. 24 (2013) 302–308.
[10] H.-H. Parving, J.B. Lewis, M. Ravid, G. Remuzzi, L.G. Hunsicker, Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective, Kidney Int. 69 (2006) 2057–2063.
[11] S.T. Knudsen, T.H. Mosbech, B. Hansen, E. Konig, P.C. Johnsen, A.L. Kamper, Screening for microalbuminuria in patients with type 2 diabetes is incomplete in general practice, Dan. Med. J. 59 (2012) A4502.
[12] J. Rungby, M. Schou, P. Warrer, L. Ytte, G.S. Andersen, Prevalence of cardiovascular disease and evaluation of standard of care in type 2 diabetes: a nationwide study in primary care, Cardiovasc. Endocrinol. 6 (2017) 145–151.
[13] P. Lange, P.W. Petersen, B. Gerdes, L. Tarnow, Management of patients with chronic obstructive lung disease, type 2 diabetes and both diseases in primary care in Denmark, Dan. Med. J. 67 (2020).
[14] M.V. Fangel, P.B. Nielsen, J.K. Kristensen, T.B. Larsen, T.F. Overvad, G.Y. Lip, M.B. Jensen, Albuminuria and risk of cardiovascular events and mortality in a general population of patients with type 2 diabetes without cardiovascular disease: a Danish cohort study, Am. J. Med. 133 (2020) e269–e279.

[15] C. Wanner, S.E. Inzucchi, J.M. Lachin, D. Fitchett, M. von Eynatten, M. Mattheus, O.E. Johansen, H.J. Woerle, U.C. Broedl, B. Zinman, Empagliflozin and progression of kidney disease in type 2 diabetes, N. Engl. J. Med. 375 (2016) 323–334.
[16] V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, K.W. Mahaffey, C.T. Investigators, Canagliflozin and renal outcomes in type 2 diabetes and nephropathy, N. Engl. J. Med. 380 (2019) 2295–2306.
[17] H.J.L. Heerspink, B.V. Stefansson, R. Correa-Rotter, G.M. Chertow, T. Greene, F.F. Hou, J.F.E. Mann, J.J.V. McMurray, M. Lindberg, P. Rossing, C.D. Sjostrom, R.D. Toto, A.M. Langkilde, D.C. Wheeler, D.-C.T. Committees, Investigators, Dapagliflozin in patients with chronic kidney disease, N. Engl. J. Med. 383 (2020) 1436–1446.
[18] J.F.E. Mann, D.D. Orsted, K. Brown-Frandsen, S.P. Marso, N.R. Poulter, S. Rasmussen, K. Tornoe, B. Zinman, J.B. Buse, L.S. Committee, Investigators, Liraglutide and renal outcomes in type 2 diabetes, N. Engl. J. Med. 377 (2017) 839–848.
[19] A.M. Warren, S.T. Knudsen, M.E. Cooper, Diabetic nephropathy: an insight into molecular mechanisms and emerging therapies, Expert Opin. Ther. Targets 23 (2019) 579–591.
[20] A. Bakke, J.G. Cooper, G. Thue, S. Skeie, S. Carlsen, I. Dalen, K.F. Lovaas, T.V. Madsen, E.R. Oord, T.J. Berg, T. Claudi, A.T. Tran, B. Gjelsvik, A.K. Jenum, S. Sandberg, Type 2 diabetes in general practice in Norway 2005-2014: moderate improvements in risk factor control but still major gaps in complication screening, BMJ Open Diabetes Res. Care 5 (2017), e000459.
[21] J.S. Knudsen, L.M. Baggesen, M. Lajer, L. Nurkanovic, A. Ustyugova, H.T. Sørensen, R.W. Thomsen, Changes in SGLT2i and GLP-1RA real-world initiator profiles following cardiovascular outcome trials: a Danish nationwide population-based study, PLoS One 15 (2020), e0229621.
[22] C.J. Sperati, S. Soman, V. Agrawal, Y. Liu, K. Abdel-Kader, C.J. Diamantidis, M.M. Estrella, K. Cavanaugh, L. Plantinga, J. Schell, J. Simon, J.A. Vassalotti, M.J. Choi, B.G. Jaar, R.C. Greer, Primary care physicians' perceptions of barriers and facilitators to management of chronic kidney disease: a mixed methods study, PLoS One 14 (2019), e0221325.
[23] A.K. Jain, M.S. Cuerden, I. McLeod, B. Hemmelgarn, A. Akbari, M. Tonelli, R.R. Quinn, M.J. Oliver, A.X. Garg, Reporting of the estimated glomerular filtration rate was associated with increased use of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in CKD, Kidney Int. 81 (2012) 1248–1253.
[24] S.T. Knudsen, J. Bodegård, K.I. Birkeland, K. Furuseth, M. Thuresson, A. Lindh, P.M. Nilsson, M. Alvarsson, M.E. Jørgensen, J. Søndergaard, F. Persson, Risk factor management of type 2 diabetic patients in primary care in the Scandinavian countries between 2003 and 2015, Prim. Care Diabetes 15 (2) (2021) 262–268.
[25] V.R. Sørensen, P.M. Hansen, J. Heaf, B. Feldt-Rasmussen, Stabilized incidence of diabetic patients referred for renal replacement therapy in Denmark, Kidney Int. 70 (2006) 187–191.
[26] P.S. Jhund, S.D. Solomon, K.F. Docherty, H.J.L. Heerspink, I.S. Anand, M. Böhm, V. Chopra, R.A. de Boer, A.S. Desai, J. Ge, M. Kitakaze, B. Merkely, E. O'Meara, M. Schou, S. Tereshchenko, S. Verma, P.N. Vinh, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, O. Bengtsson, A.M. Langkilde, M. Sjöstrand, J.J.V. McMurray, Efficacy of Dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF, Circulation 143 (4) (2021) 298–309.
[27] S.D. Anker, J. Butler, G. Filippatos, M.S. Khan, N. Marx, C.S.P. Lam, S. Schnaidt, A.P. Ofstad, M. Brueckmann, W. Jamal, E. Bocchi, P. Ponikowski, S.V. Perrone, J.L. Januzzi, S. Verma, M. Böhm, J.P. Ferreira, S.J. Pocock, F. Zannad, M. Packer, Effect of Empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status - results from the EMPEROR-reduced trial, Circulation 143 (4) (2021) 337–349.
[28] D.C. Wheeler, B.V. Stefánsson, N. Jongs, G.M. Chertow, T. Greene, F.F. Hou, J.J.V. McMurray, R. Correa-Rotter, P. Rossing, R.D. Toto, C.D. Sjöström, A.M. Langkilde, H.J.L. Heerspink, Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial, Lancet Diabetes Endocrinol. 9 (2021) 22–31.