ORIGINAL ARTICLE

Chronic kidney disease progression among patients with type 2 diabetes identified in US administrative claims: a population cohort study

Csaba P. Kovesdy 1, Danielle Isaman 2, Natalia Petruski-Ivleva 2, Linda Fried 3, Michael Blankenburg 4, Alain Gay 4, Priscilla Velentgas 2 and Kerstin Folkerts 5

1Department of Medicine, Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, USA, 2Department of Science, Aetion Inc., Boston, MA, USA, 3Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, 4Medical Affairs & Pharmacovigilance, Pharmaceuticals, Bayer AG, Berlin, Germany and 5Market Access, Public Affairs & Sustainability, HEOR CV, Bayer AG, Wuppertal, Germany

Correspondence to: Csaba P. Kovesdy; E-mail: ckovesdy@uthsc.edu

GRAPHICAL ABSTRACT

Chronic kidney disease progression among patients with type 2 diabetes identified in United States administrative claims: a population cohort study

Methods
US Administrative Claims Data
1 January 2008 – 30 September 2018
Type 2 DM + CKD

Results
Type 2 DM + CKD
CKD worsening in 10–17% of patients
Median follow-up 2 years
Approx 1/3 eGFR or 1 uACR
Median follow-up 1.5 years

Conclusion: A relatively high proportion of patients were observed with disease progression over a short period of time, highlighting the need for better identification of patients at risk of rapidly progressive CKD.

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ABSTRACT

Background. Chronic kidney disease (CKD), one of the most common complications of type 2 diabetes (T2D), is associated with poor health outcomes and high healthcare expenditures. As the CKD population increases, a better understanding of the prevalence and progression of CKD is critical. However, few contemporary studies have explored the progression of CKD relative to its onset in T2D patients using established markers derived from real-world care settings.

Methods. This retrospective, population-based cohort study assessed CKD progression among adults with T2D and with newly recognized CKD identified from US administrative claims data between 1 January 2008 and 30 September 2018. Included were patients with T2D and laboratory evidence of CKD as indicated by the established estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (UACR) criteria. Disease progression was described as transitions across the eGFR- and UACR-based stages.

Results. A total of 65,731 and 23,035 patients with T2D contributed to the analysis of eGFR- and UACR-based CKD stage progression, respectively. CKD worsening was observed in approximately 10–17% of patients over a median follow-up of 2 years. Approximately one-third of patients experienced an increase in eGFR values or a decrease in UACR values during follow-up.

Conclusions. A relatively high proportion of patients were observed with disease progression over a short period of time, highlighting the need for better identification of patients at risk of rapidly progressive CKD. Future studies are needed to determine the clinical characteristics of these patients to inform earlier diagnostic and therapeutic interventions aimed at slowing disease progression.

Keywords: chronic kidney disease, disease progression, eGFR, real-world data, type 2 diabetes, UACR

INTRODUCTION

Chronic kidney disease (CKD), a serious complication of type 2 diabetes (T2D), impacts 25–40% of the diabetic population [1, 2]. Progression of CKD is associated with poor health outcomes and can culminate in potentially fatal end-stage renal disease (ESRD) [1–3]. Dialysis, renal transplantation and the intensive care afforded to ESRD patients represent a severe strain on the healthcare system, reaching costs of nearly $34 billion in the US alone in 2015 [4]. With the diabetic population projected to grow, a substantial increase in the CKD population is expected [5]. Better understanding of the prevalence and timing of CKD progression in diabetes is needed to inform prevention and treatment strategies.

CKD prevalence is defined and classified based on the presence of persistently low kidney function and/or the presence of kidney damage for a period of at least 3 months [6, 7]. CKD is observed on average 10–20 years after the onset of T2D [8]. Established markers of CKD include persistently low estimated glomerular filtration rate (eGFR) and elevated urine albumin:creatinine ratio (UACR) [9]. eGFR and UACR values are also used to determine CKD staging, according to the Kidney Disease: Improving Clinical Outcomes (KDIGO) recommendations [6]. Guidelines recommend two or more kidney function test results at least 3 months apart to confirm a CKD diagnosis [6]. eGFR values <60 mL/min/1.73 m² and UACR values ≥30 mg/g are indicative of CKD [6]. CKD progression is operationalized as a decrease in eGFR, an increase in UACR or a combination of both over time in an individual.

Prior studies on the timing of CKD progression in real-world data are limited due to the highly variable nature of CKD, the complexity of defining the exact time of diabetes onset and the rarity of T2D cohorts with long-term observability and availability of laboratory measurements [8, 10, 11]. A US-based cohort study of 3682 participants with progressive CKD reported that patients spent a median of 7.9 years in Stage 3a, 5 years in Stage 3b, 5.2 years in Stage 4 and <1 year in Stage 5 CKD; diabetes substantially shortened these times [12]. To our knowledge, few studies have explored the feasibility of assessing CKD progression relative to its onset in T2D patients or using established markers derived from real-world administrative claims data, which provide a unique opportunity to generate evidence that is generalizable to larger populations as observed in clinical practice. We sought to assess the prevalence of newly recognized CKD and subsequent disease progression using laboratory-based markers in a large administrative claims data source.

MATERIALS AND METHODS

Data source

This was a retrospective cohort study using Optum Clininformatics Data Mart (CDM) data, a US claims database comprised of deidentified health plan data captured during the billing of routine healthcare encounters. Comprehensive longitudinal information on demographics, coded inpatient and outpatient diagnoses and procedures, outpatient prescription dispensing and laboratory results is recorded in the database. This database captures ~63 million unique members (2007–18) and is considered to be representative of the commercially insured US population [13].

Study population

The study population consisted of health plan enrollees ≥18 years of age with T2D and laboratory evidence of CKD enrolled in a health plan between 1 January 2007 and 30 September 2018. Patients must have had evidence of compromised kidney function as indicated by at least two laboratory results indicating reduced eGFR (<60 mL/min/1.73 m²) or at least two laboratory results indicating elevated UACR (≥30 mg/g) 90–365 days apart. The date of the second laboratory result confirming CKD defined the index date. Patients were required to have continuous health plan enrollment for 365 days prior to the index date (baseline period). T2D was defined as one or more inpatient International Classification of Diseases, Ninth Revision/Tenth Revision (ICD-9/10) diagnosis code for T2D, two or more outpatient ICD-9/10 diagnosis codes for T2D at least 30-
CKD progression among T2D patients

Patient characteristics
A priori patient characteristics were identified based on published literature and expert insight. Patient characteristics included demographic information, KDIGO-based eGFR and UACR stage at index [6], clinical characteristics (select cardiovascular conditions and CKD- and T2D-related diagnoses) and comediations (cardiovascular and antglycemic agents). Patient demographic data were assessed on the index date. KDIGO-based eGFR and UACR stages were assessed on the index date among patients who entered the cohort on an eGFR and/or UACR laboratory result, respectively. Then we assessed the nearest laboratory value available for the other laboratory test date among patients who entered the cohort on an eGFR and/or UACR laboratory result, respectively. Sensitivity analyses
In a sensitivity analysis, we assessed disease progression based on two eGFR test results in follow-up at least 90 days apart. Both test results in follow-up had to fall within the same CKD stage, different from the initial stage, to be considered a transition. All statistical analysis was performed using the Aetion Evidence Platform version 3.7 (Aetion, New York, NY, USA) [15].

RESULTS
Participants and patient characteristics
Among 61 199 398 patients in the database, a total of 65 731 T2D patients with newly recognized CKD had sufficient data to assess eGFR progression. A total of 23 035 patients had sufficient data to assess UACR progression (Figure 1).

Outcomes
The primary outcome was the last observed CKD stage in follow-up based on an eGFR and/or UACR laboratory result. Follow-up began on the index date and ended at the earliest occurrence of the outcome, death, end of enrollment or end of data.

Statistical analyses
Kidney function was categorized according to KDIGO guidelines for CKD staging defined by eGFR and UACR values (Supplementary data, Table S1). Only eGFR and UACR results \( \geq 0-<200 \text{mL/min/1.73 m}^2 \) and \( 3250 \text{mg/g} \), respectively, were used in this study. Outliers outside of these thresholds, calculated as 3 times the standard deviation (SD), were not considered. To capture eGFR based on serum creatinine values, we used the Chronic Kidney Disease Epidemiology Collaboration equation, applying a formula specific to the documented race of the patient. This equation has shown accuracy across diverse populations in prior research [14]. Lastly, any patients with two or more nonidentical test results on the same day (<1% of the population) were excluded from the analysis.

Frequency distributions for categorical variables and descriptive statistics for continuous variables among patients with nonmissing values were used. For claims-based variables, a lack of claims was assumed to indicate lack of the condition (e.g. comorbidities). No imputations on missing data were performed.

To identify a transition to a higher or lower CKD stage, we first identified the initial eGFR- and/or UACR-based stage on the index date. Next we identified the last observed corresponding laboratory result during the follow-up period. The number and percentage of patients transitioning from one CKD stage on the index date to another CKD stage in follow-up were cross-tabulated. The median [interquartile range (IQR)] time from the index date until the last observed laboratory result was reported in days.

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Among the 23,035 T2D patients with CKD who had sufficient data to assess UACR progression, 64% of patients had no change in UACR stage over a median follow-up of 1.3 years. Among patients at UACR Stage A2 on the index date, disease progression to the next stage was observed in 10.4% of patients over a median of 2 years. Increased UACR values were observed in 28% of patients over a median follow-up of 1.5 years and <5% of patients regressed from Stage A3 to A1 during all available follow-ups (Table 5).

Sensitivity analysis
A total of 47,938 patients had two eGFR test results during the follow-up, allowing assessment of eGFR-based disease progression using two test results. No change in eGFR stage was observed for 58–72% of patients. Disease progression from Stages 3a, 3b and 4 to the next closest stage was observed in 8.4, 5.9 and 4.7% of patients, respectively, over a median of 3 years. Improved eGFR levels were observed in ~18% of patients over a median of 2 years. Disease progression over two eGFR stages was captured in 2.0% of patients over a median of 4 years. Of patients at eGFR Stage 5 on the index date, regression to eGFR Stage 4 was observed in 8% of patients over a median of 2.3 years (Supplementary data, Table S5).

DISCUSSION
In the published literature, few studies report stage-based progression relative to a newly recognized CKD diagnosis [8]. In the years after CKD onset, the rate of eGFR decline and UACR incline is variable and can be influenced by managed therapy for hyperglycemia, hypertension and hyperlipidemia [16]. In this study, we found that 50–64% of patients with CKD and T2D showed no disease progression over a median follow-up of ~1.3 years. Approximately 10–17% of patients progressed to the next closest stage over a median follow-up of 2 years. Few (~2%) patients progressed more than one stage after a median follow-up of 3.4 years.

Results of the sensitivity analysis showed a lower rate of progression over a longer follow-up time, with approximately 5–8.4% showing a progression over a period of 3 years. This finding suggests the selection of healthier individuals with longer follow-up time needed to observe two test results or the variability of test results over time, in which fewer patients had a sustained decline as indicated by two test results in the same stage range. The presence of acute kidney injury among some patients who are classified as disease progression based on one test result is also possible.

Our findings are comparable to those reported in the existing literature [17]. For example, a study by Ruzafa et al. [17] using data from the UK primary care setting reported that roughly 10–19% of patients progressed one stage over 1.7–1.9 years of
follow-up. Authors also reported that <4% of patients progressed two stages during the study period, with a median follow-up time of 5 years.

We report that ~30% of all patients experienced improvement in eGFR or UACR values over an average follow-up of 1.5 years. While prior studies have established a strong relationship between eGFR decline and worsening CKD, the opposite may also be true. Some evidence suggests that positive eGFR slopes are associated significantly with a higher risk of ESRD and mortality [18]. Thus regression among these patients may not be actual improvement in kidney function, but rather a decrease in muscle mass that are reflected in serum creatinine levels. Weight loss among these patients usually indicates worsening of health or frailty and increases in muscle mass that are reflected in serum creatinine levels. Weight loss among these patients usually indicates worsening of health or frailty and increases in muscle mass that are reflected in serum creatinine levels.

In contrast to changing eGFR values, previous research has shown that positive eGFR slopes are also associated with a higher risk of ESRD and mortality [19]. Thus regression among these patients may not be actual improvement in kidney function, but rather a decrease in muscle mass that are reflected in serum creatinine levels. Weight loss among these patients usually indicates worsening of health or frailty and increases in muscle mass that are reflected in serum creatinine levels. Weight loss among these patients usually indicates worsening of health or frailty and increases in muscle mass that are reflected in serum creatinine levels.

In a large cohort study using Swedish Population Registry data, Carrero et al. [21] reported lower risks of ESRD among patients with greater reductions in UACR measured over 1- to 3-year intervals; significantly higher ESRD risk was observed with increases in UACR over these times. A study of diabetic patients by Jun et al. [22] that analyzed ADVANCE-ON trial data additionally reported a positive, linear association between changes in UACR over 2 years and the risk of different notably, the role of changes in renin–angiotensin system blockade treatment on increasing eGFR levels requires further investigation.

In contrast to changing eGFR values, previous research indicates that declining and increasing UACR over time results in better and worse health outcomes, respectively [20]. According to the Deyo comorbidity score, patients with greater reductions in UACR measured over 1- to 3-year intervals; significantly higher ESRD risk was observed with increases in UACR over these times. A study of diabetic patients by Jun et al. [22] that analyzed ADVANCE-ON trial data additionally reported a positive, linear association between changes in UACR over 2 years and the risk of different notably, the role of changes in renin–angiotensin system blockade treatment on increasing eGFR levels requires further investigation.

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Overall, this study adds to the existing body of literature on CKD and T2D by examining CKD disease progression and timing among T2D patients from the onset of newly recognized CKD. We observed CKD progression by eGFR- and UACR-based stages among 10–17% of patients in this study over a relatively short period of 2 years. This finding highlights a nonnegligible proportion of patients with T2D and newly recognized CKD who are expected to experience rapid disease progression and worsening health outcomes. The prompt identification of these patients is crucial to informing a vulnerable population with potential unmet therapeutic need. Future studies are needed to determine the clinical characteristics of these patients at risk of rapidly progressive CKD to inform earlier diagnostic and therapeutic interventions that slow disease progression and the need to develop better therapeutic interventions for patients at risk of rapid progression.

Several limitations common to administrative claims data existed. First, laboratory results were available for ~30% of patients in the database; only a small fraction of individuals available in the Optum database qualified for inclusion in this analysis, partly due to the necessary stringent definitions used for T2D and especially CKD and CKD progression. This reduced our sample size and may have resulted in selection bias [23]. To explore the presence of any selection bias due to the additional test result requirement in follow-up, we compared baseline patient characteristics of newly recognized CKD patients (defined by the laboratory test results criteria) and no additional test results in follow-up (n = 117,424) to patients with one additional test result included in the main analysis for eGFR progression (n = 65,731) and UACR progression (n = 23,035), as well as to those with two additional tests for eGFR included in the sensitivity analysis (n = 47,938) (Supplementary data, Table S10). We observed that patients with one and two additional tests in follow-up did not differ from patients with no test results in follow-up in terms of demographic characteristics, CKD stage at the index date, comorbidities and medication use; however, patients with two additional tests in follow-up were observed for a longer time period (median of 3 versus 1.7 years). Second, we refer to eGFR and UACR laboratory results as the gold standard for identification of renal disease [14, 24, 25]. However, there are circumstances in which any creatinine-based estimate of kidney function, including eGFR, should not be used. For example, creatinine-based estimates should be avoided in patients with changing serum creatinine values; people with acute kidney injury; people with extremes in muscle mass, body size or altered diets; and people taking medications that affect excretion of creatinine. To address this limitation, we required patients to have at least two laboratory results confirming CKD before they were classified as having the disease. We also performed sensitivity analyses to evaluate disease progression based on two test results for eGFR [6, 14, 15]. Third, the Optum CDM is considered to be representative of the commercially insured US population but may not be representative of non-US-based populations or non-commercially insured US populations. Finally, because of the limited follow-up time available in the claims data, full progression from newly recognized CKD to ESRD is unlikely to be captured. This limitation may have also impacted our ability to observe more patients with disease progression. While the maximum allowable follow-up time was ~10 years, the typical transition from Stage 1 to 5 CKD based on eGFR measurements is closer to 20 years [8].

Table 3. Baseline medication use among patients with DKD

| Medications | eGFR cohort (n = 65,731) | UACR cohort (n = 23,035) |
|-------------|-------------------------|-------------------------|
| Antiglycemic agents, n (%) | | |
| Metformin | 33,825 (51.5) | 15,503 (67.3) |
| Any second-line therapy | 33,885 (51.6) | 14,066 (61.1) |
| Sulfonylurea | 20,877 (31.8) | 8,176 (35.5) |
| Thiazolidinedione | 6,536 (9.9) | 2,089 (9.1) |
| DPP4i | 7,733 (11.2) | 3,555 (15.4) |
| SGLT2i | 9,56 (1.5) | 967 (4.2) |
| GLP1ra | 2,233 (3.4) | 1,352 (5.9) |
| Basal insulin | 10,084 (15.3) | 5,444 (23.6) |
| Any two second-line therapies* | 12,875 (19.6) | 6,342 (27.5) |
| Sulfonylurea + thiazolidinedione | 2,877 (4.4) | 991 (4.3) |
| Sulfonylurea + DPP4i | 3,009 (4.6) | 1,518 (6.6) |
| Sulfonylurea + SGLT2i | 333 (0.5) | 288 (1.3) |
| Sulfonylurea + GLP1ra | 655 (1.0) | 408 (1.8) |
| Sulfonylurea + basal insulin | 2,352 (3.6) | 1,325 (5.8) |
| Thiazolidinedione + DPP4i | 891 (1.4) | 369 (1.6) |
| Thiazolidinedione + SGLT2i | 85 (0.1) | 72 (0.3) |
| Thiazolidinedione + GLP1ra | 304 (0.5) | 151 (0.7) |
| Thiazolidinedione + basal insulin | 679 (1.0) | 302 (1.3) |
| DPP4i + SGLT2i | 275 (0.4) | 233 (1.3) |
| DPP4i + basal insulin | 979 (1.5) | 617 (2.7) |
| SGLT2i + GLP1ra | 138 (0.2) | 148 (0.6) |
| SGLT2i + basal insulin | 244 (0.4) | 127 (0.3) |
| GLP1ra + basal insulin | 530 (0.8) | 413 (1.8) |
| Combination injectable therapy* | 4,430 (6.7) | 2,191 (9.5) |
| Cardiovascular agents, n (%) | | |
| ACEI/ARB | 4,263 (68.9) | 17,075 (74.1) |
| x-blocker agent | 2,293 (5.5) | 621 (2.7) |
| x-glucosidase inhibitor | 182 (0.3) | 108 (0.5) |
| Aspirin | 527 (0.8) | 242 (1.1) |
| /-blocker | 28,921 (44.0) | 8,878 (38.5) |
| Calcium channel blocker | 20,964 (31.9) | 8,147 (35.4) |
| Centrally acting antihypertensive | 2,765 (4.2) | 797 (3.5) |
| Diuretic | 37,135 (56.5) | 9,085 (39.4) |
| Loop diuretic | 13,310 (20.2) | 2,631 (11.4) |
| Thiazide diuretic | 27,558 (41.9) | 7,120 (30.9) |
| Potassium-sparing diuretic | 7,201 (11.0) | 1,015 (4.4) |
| MRA | 3,460 (5.3) | 259 (2.3) |
| Epithelial sodium channel blocker | 3,992 (6.2) | 537 (2.3) |
| Direct renin inhibitor | 326 (0.5) | 110 (0.5) |
| HMG-CoA reductase inhibitor (statin) | 43,093 (65.6) | 15,861 (68.9) |
| Meglitinide | 663 (1.0) | 262 (1.1) |
| Oral anticoagulant | 5,917 (9.0) | 1,515 (6.6) |
| Potassium binding agent | 139 (0.2) | 22 (0.1) |

*Dual second-line therapy included drugs used concurrently for >30 days.
*bCombination injectable therapy included the concurrent use of basal and meal-time insulin for >30 days.

dPP4i: dipeptidyl peptidase-4 inhibitor; GLP1ra: glucagon-like peptide-1 receptor agonist; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose co-transporter-2 inhibitor.

Cardiovascular outcomes and all-cause mortality. Published literature suggests this relationship could plausibly be explained by underlying pathophysiologic processes including dysfunction of the vascular endothelium and chronic, low-grade inflammation [20–22]. The reported risks of major clinical outcomes and mortality associated with CKD progression support the prognostic utility of actively monitoring eGFR and UACR values over time.
Table 4. Proportion and median (IQR) time to CKD progression according to eGFR values during follow-up among patients with DKD

| Patients with available eGFR results (N = 65,731) | Last observed eGFR stage in follow-up |
|-----------------------------------------------|-------------------------------------|
| eGFR stage on index*                               | 1    | 2     | 3a  | 3b  | 4   | 5   |
| From 3a, n (%)                                   | 306 (0.6) | 14,540 (28.3) | 26,393 (51.4) | 8,694 (16.9) | 11,97 (2.3) | 179 (0.3) |
| 3b, n (%)                                        | 34 (0.3) | 1,071 (8.4) | 3,984 (31.3) | 5,914 (46.4) | 5,104 (11.8) | 213 (1.7)  |
| 4, n (%)                                         | 11 (0.7) | 74 (5.0) | 189 (12.8) | 478 (32.4) | 572 (38.6) | 150 (10.2) |
| 5, n (%)                                         | 1 (0.0) | 8 (0.6) | 21 (12.1) | 14 (8.0) | 23 (15.2) | 107 (61.5) |
| Time to transition (days)                        | 1    | 2     | 3a  | 3b  | 4   | 5   |
| From 3a, median (IQR)                            | 932 (487–1505) | 641 (285–1151) | 533 (235–1010) | 846 (402–1528) | 1243 (667–2088) | 1,705 (938, 2,407) |
| 3b, median (IQR)                                 | 744 (143–1319) | 615 (265–1163) | 526 (223–1026) | 572 (236–1094) | 850 (410–1530) | 1,232 (661, 2,004) |
| 4, median (IQR)                                  | 570 (310–1,603) | 478 (102–950) | 628 (193–1,043) | 490 (177–960) | 413 (184–812) | 632 (334, 1,215) |
| 5, median (IQR)                                  | 680 (680–680) | 639 (243–1,030) | 394 (202–755) | 291 (118–948) | 293 (33–825) | 477 (189, 854) |

*Stage 1: eGFR ≥90 mL/min/1.73 m² and UACR ≥30 mg/g; Stage 2: eGFR 60–89 mL/min/1.73 m² and UACR ≥30 mg/g; Stage 3a: eGFR 45–59 mL/min/1.73 m²; Stage 3b: eGFR 30–44 mL/min/1.73 m²; Stage 4: eGFR 15–29 mL/min/1.73 m²; Stage 5: <15 mL/min/1.73 m².

Table 5. Proportion and median (IQR) time to CKD progression according to UACR values during follow-up, among patients with DKD

| Patients with available UACR results (n = 23,035) | Last observed eGFR stage in follow-up |
|-----------------------------------------------|-------------------------------------|
| UACR category at index*                               | A1    | A2     | A3   |
| From A2, n (%)                                   | 5027 (25.8) | 12,387 (63.7) | 2033 (10.4) |
| A3, n (%)                                        | 138 (3.9) | 1106 (30.9) | 2326 (65.1) |
| Time to transition (days)                        | A1    | A2     | A3   |
| From A2, median (IQR)                            | 541 (272–935) | 487 (245–909) | 739 (381–1227) |
| A3, median (IQR)                                 | 690 (259–1,283) | 477 (241–959) | 461 (229–883) |

*A1: UACR < 30 mg/g and eGFR < 60 mL/min/1.73 m²; A2: UACR 30–299 mg/g; A3: UACR ≥300 mg/g.

SUPPLEMENTARY DATA
Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT
D.I., N.P., and P.V. were employees of Aetion and owned stock options at the time this work was conducted. C.P.K. received honoraria for consultant work from Amgen, AstraZeneca, Bayer, Takeda, Reata, Tricida and Cara Therapeutics. L.F. received honoraria from Bayer and Novo Nordisk. M.B., A.G. and K.F. are employees of Bayer AG.

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