Long-term Trends in Antidiabetes Drug Usage in the U.S.: Real-world Evidence in Patients Newly Diagnosed With Type 2 Diabetes

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OJBECTIVE

To explore temporal trends in antidiabetes drug (ADD) prescribing and intensification patterns, along with glycemic levels and comorbidities, and possible benefits of novel ADDs in delaying the need for insulin initiation in patients diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes aged 18–80 years, who initiated any ADD, were selected (*n* = 1,023,340) from the U.S. Centricity Electronic Medical Records. Those who initiated second-line ADD after first-line metformin were identified (subcohort 1, *n* = 357,482); the third-line therapy choices were further explored.

RESULTS

From 2005 to 2016, first-line use increased for metformin (60–77%) and decreased for sulfonylureas (20–8%). During a mean follow-up of 3.4 years post metformin, 48% initiated a second ADD at a mean HbA_{1c} of 8.4%. In subcohort 1, although sulfonylurea usage as second-line treatment decreased (60–46%), it remained the most popular second ADD choice. Use increased for insulin (7–17%) and dipeptidyl peptidase-4 inhibitors (DPP-4i) (0.4–21%). The rates of intensification with insulin and sulfonylureas did not decline over the last 10 years. The restricted mean time to insulin initiation was marginally longer in second-line DPP-4i (7.1 years) and in the glucagon-like peptide 1 receptor agonist group (6.6 years) compared with sulfonylurea (6.3 years, $P < 0.05$).

CONCLUSIONS

Most patients initiate second-line therapy at elevated HbA_{1c} levels, with highly heterogeneous clinical characteristics across ADD classes. Despite the introduction of newer therapies, sulfonylureas remained the most popular second-line agent, and the rates of intensification with sulfonylureas and insulin remained consistent over time. The incretin-based therapies were associated with a small delay in the need for therapy intensification compared with sulfonylureas.

A broad choice of "old" and "new" antidiabetes drugs (ADDs) is available, which differ not only in their mechanisms of action but also in their glycemic and extraglycemic effects (1). While treatment guidelines for type 2 diabetes are regularly updated based on new evidence, real-world prescription trends may also be driven by other factors, such as medication costs, side effect profile, and provider and patient preferences.

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With the development of new classes of antidiabetes therapies since 2005, including incretin-based drugs and sodium–glucose cotransporter 2 inhibitors (SGLT2i), the paradigm of therapy options for patients with highly heterogeneous glycemic and cardiovascular risk factors has changed significantly. However, the way in which this has occurred in real-world practice, especially in the trade-off between older and new classes of ADDs as initial and intensification therapy options, has not been studied thoroughly.

The newer ADDs have been shown to be associated with significantly lower risk of hypoglycemia compared with the sulfonylureas (SU) and insulin (INS) (2). The weight neutrality or benefits of weight reductions have also been well established for new therapies including the incretins (3,4). Given the glycemic and extraglycemic benefits of these agents, one would expect a fall in the use of SU or INS as intensification therapies. However, studies evaluating the possible benefits of using newer ADDs in terms of delaying the need for INS are scarce (5,6). In this context, understanding the changing patterns of therapy initiation and intensifications with second- and third-line therapies, in conjunction with the heterogeneous patients' characteristics, is a fundamental background requirement.

Cohen et al. (7) explored ADD-prescribing patterns in the U.S. from 1997 to 2000 and reported decreasing use of SU and increasing trends in metformin (MET) and thiazolidinedione (TZD) prescription over time. Utilizing a claims database, Desai et al. (8) reported an increasing proportional share of MET and decreasing prescriptions for TZD between 2006 and 2008. One of the reasons for the reduction in the use of TZD was the safety concerns (9–12). While Berkowitz et al. (13) evaluated treatment initiations with MET, SU, and dipeptidyl peptidase-4 inhibitors (DPP-4i) between 2009 to 2013 in the U.S., utilization patterns of other ADDs and the changing utilization trend over time were not explored (14). Lipska et al. (15) have evaluated the temporal trend in the use of ADDs from 2006 to 2013 using claims data from the U.S. A small number of studies have explored the clinical characteristics of patients according to the type of ADD prescribed, but only over relatively short time periods, and did not evaluate treatment intensification with second- or third-line ADDs over a long period of time (16,17).

To the best of our knowledge, the progressive changes in the proportional distributions across all new and old ADDs, and the patterns and determinants of therapy intensification with second- and third-line ADDs, have not been explored comprehensively in any study. With recognition of the growing disease burden and increasing volumes of dispensed medications (18–21), the primary aim of this study was to provide a comprehensive up-to-date exploration of the treatment pattern changes for type 2 diabetes in the U.S. using the nationally representative Centricity Electronic Medical Records (CEMR) from primary and secondary ambulatory care systems. Specifically, the aims were to *1*) explore temporal changes in prescribing patterns from 2005 to 2016 with respect to the drug initiation order, *2*) explore therapy intensification with second and third ADDs, *3*) explore patient characteristics including risk factors and comorbidities according to ADD therapy prescribed, *4*) explore the temporal patterns in the rates of intensification with SU and INS, and *5*) evaluate whether use of incretin-based therapies as second-line therapy delays the need for intensification with third-line ADDs and with INS any time during follow-up.

RESEARCH DESIGN AND METHODS

Data Source

CEMR represents a variety of ambulatory and primary care medical practices, including solo practitioners, community clinics, academic medical centers, and large integrated delivery networks in the U.S. More than 34 million individuals' longitudinal electronic medical records (EMRs) were available from 1995 to April 2016. More than 35,000 physicians and other providers from all U.S. states contribute to the CEMR, of whom ~75% are primary care providers. The database is generally representative of the U.S. population, with a diabetes prevalence of 7.1% (identified by diagnostic codes) that is similar to the national diabetes prevalence of 6.7% (diagnosed diabetes in 2014) (14). The CEMR has been used extensively for academic research worldwide (3,22,23).

This database contains comprehensive patient-level information on demographic, anthropometric, clinical, and laboratory variables including age, sex, ethnicity, and longitudinal measures of BMI, blood pressure, glycated hemoglobin (HbA_{1c}), and lipids. All disease events along with dates are coded with ICD-9, ICD-10, or SNOMED CT codes. Medication data include brand names and doses for individual medications prescribed, along with start/stop dates and specific fields to track treatment alterations. This data set also contains patient-reported medications, including prescriptions received outside the EMR network and over-the-counter medications.

Methods

Eleven antidiabetes therapeutic classes were considered in this study: MET, SU, TZD, α-glucosidase inhibitors (AGI), amylin, dopamine receptor agonists (DOPRA), meglitinides (MEG), DPP-4i, glucagon-like peptide 1 receptor agonists (GLP-1RA), SGLT2i, and INS. For each patient, these ADDs were arranged chronologically according to the initiation dates. Same-day initiations (including combination therapies) were prioritized in the order as listed above, with highest order priority assigned to MET and lowest to INS. Additions or switches were defined by comparing stop dates and start dates of corresponding therapies. Details on the medication data structure, associated data-mining challenges, and description of an algorithm applied to extract and aggregate patient-level medication data from CEMR have recently been published (24).

For convenience, AGI, amylin, DOPRA, and MEG were combined into the "other" category. Saxenda (a version of liraglutide) was excluded from the GLP-1RA list, as it was approved in 2014 for weight lowering and not as an ADD (25). Although Welchol (colesevelam) was approved for the treatment of type 2 diabetes, it was mainly prescribed to reduce cholesterol levels; therefore, we did not include colesevelam in our analyses (18).

Patients with diabetes were identified on the basis of diagnostic codes; those with a diagnosis of type 1 diabetes or only gestational diabetes mellitus were identified and excluded. For identified patients with type 2 diabetes, the following inclusion criteria were applied: *1*) age at diagnosis $\geq$18 and $<$80 years, *2*) diagnosis date strictly after first registered activity in the database, *3*) diagnosis date on or after 1 January 2005, and *4*) initiation of any ADD.

Demographic variables included sex, age, and ethnicity. HbA_{1c} values on the

date of diagnosis and first-, second-, and third-line ADD therapy initiation were obtained as the closest observations within a 3-month window. Body weight, BMI, systolic/diastolic blood pressure (SBP/DBP), lipids (LDL, HDL, and triglycerides), and heart rate were calculated as the average of available measurements within a 3-month window of the diagnosis or ADD initiation date. Obesity was defined as BMI $\geq$30 kg/m^2.

The presence of comorbidities prior to the first and second drug initiation was explored. Cardiovascular disease (CVD) was defined as ischemic heart disease (including myocardial infarction), peripheral vascular disease, heart failure, or stroke. Cancer was defined as any malignancy except malignant neoplasm of skin. Charlson Comorbidity Index was defined and calculated following the algorithm described by Quan et al. (26).

Statistical Methods

The characteristics of patients were summarized by ADD classes—at first prescription and at second ADD initiation when added to MET. Separate analyses were conducted to explore the pattern of addition or switch to third ADD by major classes of second-line ADDs. Study variables were summarized as number (%), mean (SD), or median (first quartile [Q1], third quartile [Q3]) as appropriate. In patients who had a second-line ADD added after MET, and had at least 1 year of follow-up post–second-line initiation, the "restricted mean survival time" estimation approach was used to compare the mean time to the third ADD/INS initiation among major second-line ADD groups. This method computes survival time as time to third ADD/INS if initiated, and otherwise as time to the end of follow-up (date of patient's last available record within the database). Standard life table methods were used to estimate rates per 100 person-years (95% CI) of second-line ADD, INS, and SU initiations in patients with a minimum of 1 year follow-up post–MET initiation.

RESULTS

From the 2,624,954 patients identified with type 2 diabetes, 2,590,853 were aged between $\geq$18 and $<$80 years at the date of diagnosis with mean/median 3.9/2.7 years of follow-up. Of these patients, 1,305,686 (50%) were newly diagnosed after 1 January 2005, while 1,023,340 patients initiated any ADD (study cohort) (Supplementary Fig. 1) during the available mean/median 3.4/2.8 years of follow-up time. In the study cohort, 46% were male, mean (SD) age was 58 years (13), and 68% were white Caucasians, 12% blacks, and 2% Asians (Table 1).

First ADD

Prescription Pattern Changes Over Time

Figure 1*A* presents the proportional distribution of the first-line ADD by year of initiation. The proportional share of MET as the first choice increased consistently from 60% in 2005 to 77% in 2016 (first quarter of the year). SU's share declined from 20 to 8%, while INS's share ranged from 8 to 10%. Starting at 11% in 2005, TZD's proportional share dropped progressively to 0.7% in 2016. Other drugs were chosen as first-line in 3% of cases or less.

Patients' Characteristics

In the study cohort of 1,023,340 patients, the distribution of prescription patterns for individual ADDs at any time from January 2005 to April 2016 and as the first ADD are presented in Table 1. The demographic and clinical characteristics of the patients, along with the prevalence of comorbidities at the time of first ADD initiation, are also presented in Table 1.

In the study cohort, 79% received MET any time during the recorded follow-up, and 72% received MET as the first ADD. The mean time to initiation of MET as the first ADD and the available follow-up time since initiation were 3.7 months and 3.3 years, respectively. The proportions of patients with HbA_{1c} level $\geq$7.5% (58 mmol/mol) and 8% (64 mmol/mol) at MET initiation were 48% and 37%, respectively. Those who initiated with GLP-1RA, DPP-4i, TZD, and SU had a similar mean HbA_{1c} of 8.0, 7.7, 7.8, and 8.0%, respectively (64, 61, 62, and 64 mmol/mol). INS was initiated at an average HbA_{1c} of 8.9% (74 mmol/mol), with 71% and 59% having HbA_{1c} $\geq$7.5% (58 mmol/mol) and 8% (64 mmol/mol), respectively.

Patients who initiated treatment with MET were younger (mean age 57 years, with 19% $\geq$70 years) than those who initiated with SU (mean age 64 years, 43% $\geq$70 years), with INS (mean 60 years, 29% $\geq$70 years), with TZD (mean 62 years, 32% $\geq$70 years), or with DPP-4i (mean 64 years, 39% $\geq$70 years). Those who had GLP-1RA and SGLT2i as the first ADD were younger, more likely to be white Caucasian, female, and obese, as compared with those who initiated with MET, DPP-4i, INS, TZD, or SU.

Comorbidities

The proportions of patients with CVD, chronic kidney disease (CKD), cancer, or depression at first ADD initiation were 19%, 4%, 4%, and 11%, respectively. Those patients initiating therapy with INS had a significantly higher prevalence of CVD (27%, $P < 0.01$), CKD (11%, $P < 0.01$), and higher Charlson Comorbidity Index with mean (SD) of 1.84 (1.31), compared with those initiating with MET, DPP-4i, GLP-1RA, or TZD (Table 1 for comparative estimates).

Discontinuation of First ADD

Among patients with at least 1 year of follow-up (n = 813,826), the proportions of patients discontinuing the first-line ADD within 1 year by individual ADDs are presented in Table 1. While only 8% of patients discontinued MET within a year, 20%, 17%, and 25% of patients discontinued GLP-1RA, DPP-4i, and SGLT2i within a year, respectively.

Second ADD

Among 740,478 patients who initiated therapy with MET, 357,482 (48%, subcohort 1) (Supplementary Fig. 1) initiated a second ADD, with an annual mean rate of 10.7 initiations per 100 person-years (minimum 10.2, maximum 14.0) during a mean 3.3 years of available follow-up, at an average HbA_{1c} level of 8.4% (68 mmol/mol), with 60% and 48% having HbA_{1c} $\geq$7.5% (58 mmol/mol) and 8.0% (64 mmol/mol), respectively. The proportional share of second-line ADD (post-MET) over time is presented in Fig. 1*B*. The demographic and clinical characteristics of the patients along with the time to second ADD, and the prevalence of comorbidities at the time of second drug initiation, are presented in Table 2.

Although the proportional share of SU as a second-line therapy gradually decreased from 60 to 46% over time (Fig. 1*B*), it remained the most popular choice (53%) of therapy intensification post–MET initiation across the whole time period. SU was initiated as second-line ADD at an average HbA_{1c} level of 8.4% (68 mmol/mol), with 62% and 49% having HbA_{1c} $\geq$7.5% (58 mmol/mol) and 8.0% (64 mmol/mol), respectively (Table 2). Among patients with a second ADD and a minimum 1 year of follow-up, only

Table 1—Patient characteristics at the time of first ADD initiation, by drug class in the study cohort (*N* = 1,023,340)

	GLP-1RA	SGLT2i	MET	INS	TZD	DPP-4i	SU	Other§	All
Any time during follow-up									
n (% of *N*)	68,522 (7)	39,549 (4)	808,518 (79)	270,432 (26)	109,754 (11)	182,457 (18)	354,367 (35)	25,358 (2)	1,023,340 (100)
Time to first prescription, months*	22.32 (27.23)	39.64 (33.48)	5.3 (14.16)	13.03 (22.54)	8.93 (17.72)	19.57 (25.56)	11.09 (20.25)	14.97 (23.56)	—
At first ADD									
*n*2 (% of *N*)	9,494 (1)	1,935 (0.2)	740,478 (72)	93,078 (9)	28,004 (3)	25,005 (2)	116,435 (11)	8,911 (1)	—
Time to first prescription, months*	3.82 (11.92)	7.94 (18.68)	3.73 (11.78)	3.74 (11.06)	2.33 (8.2)	4.98 (13.65)	3.84 (11.51)	2.45 (9.66)	3.73 (11.66)
Follow-up from ADD initiation, years*	3.22 (2.5)	0.98 (0.62)	3.31 (2.54)	2.94 (2.45)	5.06 (3.02)	2.79 (2.1)	3.72 (2.7)	3.86 (2.71)	3.36 (2.58)
Follow-up ≥1 year from first ADD initiation, *n*3 (% of *n*2)	7,400 (78)	889 (46)	589,246 (80)	68,385 (73)	25,105 (90)	19,278 (77)	95,854 (82)	7,669 (86)	813,826 (80)
Discontinuation within 1 year, *n* (% of *n*3)	1,516 (20)	225 (25)	44,485 (8)	3,359 (5)	4,795 (19)	3,243 (17)	9,765 (10)	1,367 (18)	68,755 (8)
Age (years)*	55 (12)	56 (11)	57 (13)	60 (13)	62 (11)	64 (11)	64 (11)	58 (16)	58 (13)
Age ≥70 years, *n* (% of *n*2)	1,217 (13)	223 (12)	144,210 (19)	26,790 (29)	8,838 (32)	9,741 (39)	50,280 (43)	2,925 (33)	244,224 (24)
Male, *n* (% of *n*2)	3,205 (34)	849 (44)	332,206 (45)	44,016 (47)	14,075 (50)	10,968 (44)	59,208 (51)	3,339 (37)	467,866 (46)
White Caucasian, *n* (% of *n*2)	7,005 (74)	1,430 (74)	512,521 (69)	58,396 (63)	18,342 (65)	17,082 (68)	77,533 (67)	5,812 (65)	698,121 (68)
Black, *n* (% of *n*2)	899 (9)	218 (11)	83,767 (11)	14,089 (15)	2,795 (10)	2,957 (12)	13,988 (12)	944 (11)	119,657 (12)
HbA_{1c}, %*	8 (1.6)	8.1 (1.7)	8.1 (1.8)	8.9 (2.1)	7.8 (1.6)	7.7 (1.5)	8 (1.6)	7.8 (1.5)	8.2 (1.8)
HbA_{1c}, mmol/mol‡	64	65	65	74	62	61	64	62	66
HbA_{1c} ≥7.5% (58 mmol/mol), *n* (% of *n*2)	831 (47)	295 (51)	108,114 (48)	19,756 (71)	2,249 (42)	2,410 (40)	15,109 (49)	509 (45)	149,273 (50)
HbA_{1c} ≥8% (64 mmol/mol), *n* (% of *n*2)	609 (34)	209 (36)	82,914 (37)	16,284 (59)	1,565 (29)	1,656 (28)	10,900 (36)	348 (31)	114,485 (39)
Weight, kg*	107.6 (26.6)	103.5 (24.8)	98.2 (24.9)	95.3 (25.3)	96.7 (25.2)	92.8 (24)	93.6 (23.7)	87.6 (24.6)	97.3 (24.9)
BMI, kg/m^2*	38.1 (8.5)	36.2 (8)	34.6 (7.9)	33.6 (8.3)	34 (7.9)	33 (7.6)	33.1 (7.6)	31.5 (8)	34.3 (7.9)
Obese, *n* (% of *n*2)	6,460 (85)	1,281 (78)	427,651 (70)	43,030 (64)	12,954 (66)	12,106 (62)	53,029 (62)	3,476 (51)	559,987 (68)
SBP, mmHg*	129 (15)	129 (14)	131 (15)	131 (18)	131 (16)	130 (16)	132 (17)	126 (17)	131 (16)
SBP ≥140 mmHg, *n* (% of *n*2)	1,538 (21)	345 (22)	153,062 (25)	20,320 (29)	5,400 (27)	4,960 (25)	26,435 (30)	1,313 (19)	213,373 (26)
DBP, mmHg*	78 (10)	78 (9)	78 (10)	75 (11)	75 (10)	75 (10)	75 (10)	74 (10)	77 (10)
Heart rate, bpm*	79 (11)	79 (12)	78 (12)	78 (12)	75 (12)	76 (12)	76 (12)	76 (11)	78 (12)
LDL, mg/dL*	103 (37)	106 (39)	106 (37)	98 (40)	100 (38)	99 (37)	98 (37)	98 (37)	104 (37)
HDL, mg/dL*	45 (13)	45 (14)	44 (13)	44 (15)	46 (14)	45 (14)	44 (14)	48 (15)	44 (13)
Triglycerides, mg/dL†	140 (102, 187)	144 (104, 195)	143 (104, 193)	133 (93, 184)	131 (94, 182)	141 (102, 188)	142 (103, 192)	123 (88, 174)	142 (103, 192)
CVD, *n* (% of *n*2)	1,422 (15)	331 (17)	118,342 (16)	25,051 (27)	5,446 (19)	6,182 (25)	31,293 (27)	1,815 (20)	189,882 (19)
CKD, *n* (% of *n*2)	377 (4)	47 (2)	12,590 (2)	10,329 (11)	1,820 (6)	2,371 (9)	10,988 (9)	643 (7)	39,165 (4)
Cancer, *n* (% of *n*2)	289 (3)	64 (3)	30,195 (4)	3,636 (4)	1,374 (5)	1,340 (5)	6,551 (6)	451 (5)	43,900 (4)
Depression, *n* (% of *n*2)	1,266 (13)	213 (11)	88,673 (12)	7,834 (8)	2,210 (8)	2,327 (9)	8,931 (8)	845 (9)	112,299 (11)
Charlson Comorbidity Index*	1.47 (0.9)	1.45 (0.91)	1.44 (0.89)	1.84 (1.31)	1.57 (1.06)	1.76 (1.22)	1.77 (1.23)	1.66 (1.16)	1.53 (1.0)

bpm, beats per minute; *n*2, number of study cohort patients prescribed each drug class as a first ADD; *n*3, number of *n*2 patients with ≥1 year follow-up after first ADD initiation. *Mean (SD); †median (interquartile range); ‡mean; §other: amylin, DOPRA, AGI, or MEG.

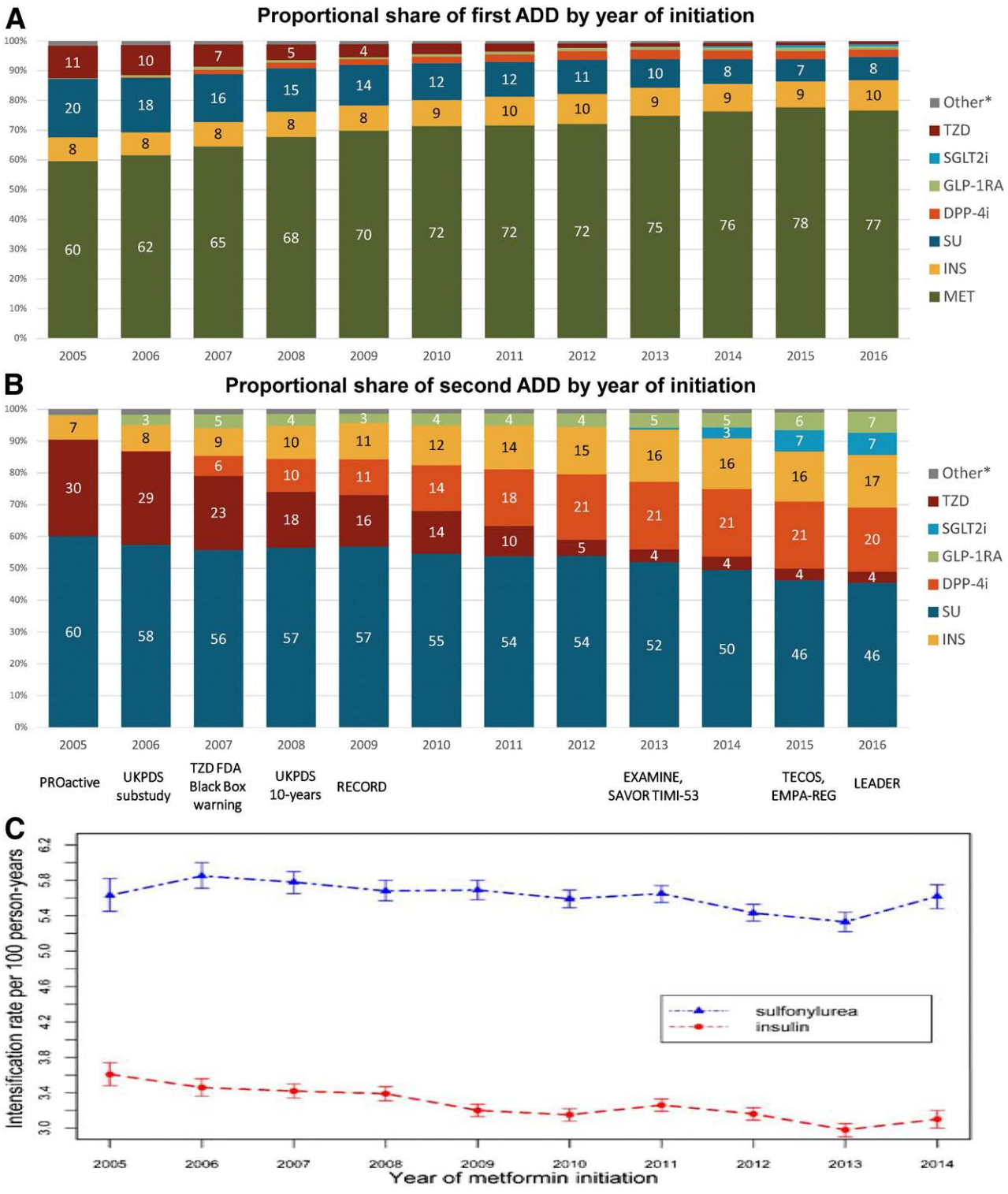

Figure 1—*A*: Proportional share of the first ADD by year of initiation in the study cohort. *B*: Proportional share of the second ADD by year of initiation in subcohort 1 and key studies listed. *C*: In patients with a minimum of 1 year of follow-up post-MET, annual rates (95% CI) of SU and INS initiations per 100 person-years. Subcohort 1: initiated second ADD and had MET as first-line treatment. *Other: amylin, DOPRA, AGI, or MEG. EMPA REG, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; FDA, U.S. Food and Drug Administration; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, UK Prospective Diabetes Study.

Table 2—Patient characteristics at the time of the second ADD initiation, by drug class added in subcohort 1‖ (*N* = 357,482)

	GLP-1RA	SGLT2i	INS	TZD	DPP-4i	SU	Other§	All
*n*1 (% of *N*)	15,448 (4)	5,971 (2)	49,939 (14)	33,021 (9)	61,508 (17)	187,819 (53)	3,776 (1)	357,482 (100)
Time from first to second ADD (months)*	11.1 (18.58)	18.52 (23.73)	5.74 (14.58)	4.09 (11.19)	11.15 (18.95)	7.38 (16.08)	7.35 (15.92)	7.84 (16.5)
Follow-up from second ADD initiation (years)*	2.97 (2.44)	0.95 (0.66)	2.71 (2.26)	4.77 (2.98)	2.68 (2.01)	3.34 (2.56)	3.59 (2.65)	3.22 (2.53)
Follow-up ≥1 year from second ADD initiation, *n*2 (% of *n*1)	11,431 (74)	2,558 (43)	36,337 (73)	28,841 (87)	46,822 (76)	149,109 (79)	3,090 (82)	278,188 (78)
Discontinuation within 1 year, *n* (% of *n*2)	2,407 (21)	643 (25)	2,537 (7)	5,913 (21)	8,234 (18)	15,569 (10)	724 (23)	36,027 (13)
Age (years)*	53 (12)	54 (11)	57 (13)	58 (11)	58 (12)	60 (12)	61 (12)	59 (12)
Age ≥70 years, *n* (% of *n*1)	1,203 (8)	435 (7)	9,576 (19)	6,450 (20)	11,595 (19)	47,416 (25)	1,116 (30)	77,791 (22)
Male, *n* (% of *n*1)	5,305 (34)	2,909 (49)	23,366 (47)	17,301 (52)	29,463 (48)	97,730 (52)	1,664 (44)	177,738 (50)
White Caucasian, *n* (% of *n*1)	11,698 (76)	4,622 (77)	33,215 (67)	22,710 (69)	43,076 (70)	130,418 (69)	2,575 (68)	248,314 (69)
HbA_{1c}, %*	7.8 (1.6)	8.1 (1.8)	9.3 (2.3)	7.9 (1.7)	8.2 (1.7)	8.4 (1.8)	7.5 (1.6)	8.4 (1.9)
HbA_{1c}, mmol/mol‡	62	65	78	63	66	68	58	68
HbA_{1c} ≥7.5% (58 mmol/mol), *n* (% of *n*1)	3,890 (44)	2,102 (59)	19,083 (73)	8,150 (46)	20,960 (57)	65,980 (62)	587 (41)	118,063 (60)
HbA_{1c} ≥8% (64 mmol/mol), *n* (% of *n*1)	2,913 (33)	1,581 (44)	16,871 (64)	6,106 (34)	15,768 (43)	51,841 (49)	418 (29)	93,499 (48)
Weight, kg*	108.1 (25.9)	105.1 (25.2)	99.8 (26)	99.9 (24.3)	98 (24.2)	98 (24.6)	94 (26.1)	98.9 (24.9)
BMI, kg/m^2*	38.1 (8.2)	36.2 (7.8)	35 (8.3)	34.8 (7.8)	34.3 (7.6)	34.3 (7.7)	33.3 (7.9)	34.6 (7.8)
Obese, *n* (% of *n*1)	12,429 (86)	4,387 (79)	32,472 (71)	20,920 (71)	39,574 (69)	117,232 (68)	1,961 (61)	222,627 (70)
SBP, mmHg*	128 (14)	129 (14)	131 (16)	130 (15)	130 (14)	132 (15)	129 (15)	131 (15)
SBP ≥140 mmHg, *n* (% of *n*1)	2,565 (18)	1,098 (20)	11,642 (25)	6,993 (24)	12,446 (22)	46,191 (27)	703 (22)	79,837 (25)
DBP, mmHg*	78 (9)	79 (9)	76 (10)	77 (9)	78 (9)	77 (10)	75 (9)	77 (9)
Heart rate, bpm*	81 (11)	80 (12)	80 (12)	78 (11)	79 (11)	79 (12)	78 (12)	79 (12)
LDL, mg/dL*	96 (34)	79 (9)	98 (37)	97 (35)	98 (35)	97 (35)	75 (9)	97 (35)
HDL, mg/dL*	44 (12)	43 (12)	43 (13)	45 (13)	44 (12)	43 (12)	47 (15)	43 (12)
Triglycerides, mg/dL†	150 (109, 200)	156 (115, 207)	143 (103, 196)	139 (100, 190)	148 (109, 197)	149 (109, 199)	135 (97, 185)	147 (107, 197)
CVD, *n* (% of *n*1)	2,134 (14)	1,004 (17)	11,781 (24)	5,894 (18)	12,212 (20)	41,220 (22)	876 (23)	75,121 (21)
CKD, *n* (% of *n*1)	301 (2)	128 (2)	1,686 (3)	836 (3)	2,090 (3)	6,806 (4)	140 (4)	11,987 (3)
Cancer, *n* (% of *n*1)	606 (4)	264 (4)	2,554 (5)	1,350 (4)	3,359 (5)	9,472 (5)	237 (6)	17,842 (5)
Depression, *n* (% of *n*1)	2,979 (19)	1,123 (19)	7,294 (15)	3,710 (11)	9,073 (15)	23,433 (12)	465 (12)	48,077 (13)
Charlson Comorbidity Index*	1.52 (0.9)	1.58 0.0(1)	1.71 (1.16)	1.48 (0.92)	1.63 (1.08)	1.63 (1.08)	1.69 (1.11)	1.62 (1.07)

bpm, beats per minute; *n*1, number of subcohort 1 patients prescribed each drug class as a second ADD; *n*2, number of *n*1 patients with ≥1 year follow-up after second ADD initiation. *Mean (SD); †median (interquartile range); ‡mean; §other: amylin, DOPRA, AGI, or MEG; ‖subcohort 1: initiated second ADD and had MET as first-line treatment.

10% discontinued SU within 1 year compared with significantly higher discontinuation proportions in other second-line non-INS ADDs.

The proportional share of DPP-4i as a therapy intensification option post–MET initiation sharply increased from 0.4% in 2006 (approved in October 2006) to 20% in 2016 (Fig. 1*B*). DPP-4i were initiated at an average HbA_{1c} of 8.2% (66 mmol/mol), with 57% and 43% having $HbA_{1c} \geq 7.5\%$ (58 mmol/mol) and 8.0% (64 mmol/mol), respectively. While 18% discontinued DPP-4i within a year of initiation, the proportions of patients discontinuing second-line GLP-1RA, TZD, or SGLT2i within a year were higher.

The proportional share of patients receiving GLP-1RA as a second ADD increased from 3% in 2006 to 7% in 2016. Initiation of GLP-1RA occurred at relatively lower HbA_{1c} levels of 7.8% (62 mmol/mol) and at the highest BMI levels among second-line ADD groups. Twenty-one percent of patients discontinued GLP-1RA therapy within a year of commencing it as a second ADD. After approval of the first SGLT2i in 2013, the proportional share of those receiving it as a second ADD reached 7% in 2016. One-quarter of patients discontinued SGLT2i therapy within a year of adding it as second-line ADD. The proportional share of patients receiving TZD as a second-line therapy dropped from 30 to 4% (Fig. 1*B*), with 21% of patients discontinuing therapy within 1 year.

The proportional share of patients receiving INS as a second ADD post–MET initiation has consistently increased from 7% in 2005 to 17% in 2016 (Fig. 1*B*). The intensification with INS occurred at a 9.3% (78 mmol/mol) average HbA_{1c} level, with 73% and 64% having $HbA_{1c} \geq 7.5\%$ (58 mmol/mol) and 8.0% (64 mmol/mol), respectively. Only 7% patients discontinued INS within 1 year of initiation.

Third ADD

Among patients in subcohort 1, 78% had at least 1 year of follow-up from the second ADD initiation (subcohort 2; *n* = 278,188). Of these patients, 144,106 (52%) initiated a third ADD, with an annual mean rate of 12.6 initiations per 100 person-years (minimum 11.4, maximum 14.9) during a mean follow-up of 4 years post–second-line initiation. Table 3 presents treatment intensification patterns by the major second-line ADDs. Most of the patients (84% [*n* = 121,559]) added a third drug on top of the second ADD, while 16% (*n* = 22,547) ceased the second ADD and switched to a third ADD. Addition of the third drug occurred at higher HbA_{1c} levels (8.5% [69 mmol/mol]) compared with switching (8.2% [66 mmol/mol]).

Among patients with SU as the second ADD, 49% (*n* = 73,776) added and 6% (*n* = 8,204) switched to a third drug during a mean follow-up of 4.1 years. The most popular third ADD addition was DPP-4i (34% of those who added a third ADD), followed by INS (28%) and TZD (26%). Among those who switched, almost one-half (49%) switched to INS, while 30% and 8% switched to DPP-4i and GLP-1RA, respectively.

SU, DPP-4i, and GLP-1RA were added to INS in 32%, 26%, and 22% of patients (from those who added a third ADD), respectively. Only 3% of patients ceased INS therapy to switch to another ADD during a mean 3.6 years of follow-up. In the second-line DPP-4i group (*n* = 46,822), 40% added and 11% switched to a third drug during a mean 3.4 years of follow-up. The most popular third ADD addition was SU (40% of those who added a third ADD), followed by INS (29%) and GLP-1RA (9%). Of those who switched from DPP-4i, one-half of the patients moved to SU, followed by INS and GLP-1RA (17%).

Among those who had a GLP-1RA as the second ADD, 52% added INS (of those who added a third ADD) and 18% switched to INS (of those who switched to a third ADD) during a mean 3.9 years of follow-up; 11% added and 34% switched to DPP-4i. In the TZD group, 43% added and 22% switched to a third ADD during 5.4 years of follow-up. Among those who switched, 45% chose SU while 35% moved to DPP-4i.

Temporal Changes in Rates of Intensification With SU and INS

Among patients with first-line MET and a minimum 1 year of follow-up, the annual rates per 100 person-years of INS/SU initiation (irrespective of order of therapy intensification) are presented in Fig. 1*C*. The rates did not significantly decline from 2005 to 2014.

Do Novel ADDs Help Delay the Need for Therapy Intensification?

The Kaplan-Meier analyses, based on restricted mean years to adding or moving to a third ADD, in major second-line ADD groups are presented in Table 3. The mean time to intensification with a third ADD was marginally longer in incretin groups (DPP-4i 4.1 years [95% CI 4.1, 4.2] and GLP-1RA 4.2 years [4.1, 4.3]) compared with that in patients with SU as the second-line ADD (3.9 years [3.8, 3.9]; $P = 0.04$). The restricted mean times to intensification with INS any time during follow-up were 6.3, 7.1, and 6.6 years in the SU, DPP-4i, and GLP-1RA groups, respectively (all comparative $P < 0.05$).

CONCLUSIONS

This longitudinal exploratory study of a large cohort of patients with type 2 diabetes observed between 2005 and 2016 from primary and ambulatory care systems in the U.S. provides *1*) a detailed account of glycemic states, clinical characteristics, and comorbidities at first-line and second-line therapy initiation by different drug classes, as well as new insights into *2*) the changes in the choice of first- and second-line ADDs over the last 10 years, *3*) patterns of therapy intensification with third-line ADDs and with INS, separately for major second-line ADDs, *4*) changes in the annual rates of therapy intensification with SU and INS over time, and *5*) possible benefits of using newer novel antidiabetes therapies in terms of delaying the need for third-line therapy intensification, including the need for initiating INS.

With 3.4 years of mean follow-up in more than one million patients with a diagnosis of type 2 diabetes from 2005, this study provides robust and detailed information on the changing clinical practices for the management of type 2 diabetes in a real-world setting. We are not aware of any study that simultaneously evaluated the changing prescribing patterns of old and new ADDs as first-line therapy and as intensification options at various levels of glycemia and comorbidities.

The proportional share of MET as the first-line therapy choice has increased from 60 to 77%, while that for SU has decreased from 20 to 8%, over the last decade. However, SU continue to be the most popular second-line therapy intensification option, although with a declining share (from 60 to 46% over the last decade). The discontinuation rate of SU was found to be the lowest among non-INS second-line ADDs. Among those who intensified with a third-line therapy, the ratio of addition to switching to third ADD

Table 3—Intensification of major second-line therapies in subcohort 2‡ (*N* = 278,188)

	GLP-1RA	INS	TZD	DPP-4i	SU	All
N	11,431	36,337	28,841	46,822	149,109	278,188
Follow-up from second ADD initiation, years*	3.85 (2.24)	3.56 (2.09)	5.40 (2.66)	3.37 (1.81)	4.09 (2.35)	4.02 (2.33)
Initiated third ADD, *n* (% of *N*)	5,942 (52)	10,677 (29)	18,788 (65)	23,840 (51)	81,980 (55)	144,106
Initiated INS, *n* (% of *N*)	3,285 (29)		8,223 (29)	9,633 (21)	45,293 (30)	67,812
Restricted mean time to a third ADD, years§	4.23 (4.14, 4.32)	6.15 (6.09, 6.21)	3.53 (3.49, 3.58)	4.12 (4.07, 4.17)	3.91 (3.88, 3.93)	4.18 (4.17, 4.20)
Restricted mean time to INS, years§	6.58 (6.49, 6.67)		6.82 (6.78, 6.87)	7.14 (7.09, 7.18)	6.26 (6.23, 6.28)	6.51 (6.49, 6.53)
Added third ADD						
*n*1 (% of *N*)	4,522 (40)	9,675 (27)	12,481 (43)	18,881 (40)	73,776 (49)	121,559 (44)
HbA_{1c}, %*	8.2 (1.7)	8.9 (2)	8.1 (1.8)	8.5 (1.8)	8.6 (1.7)	8.5 (1.8)
HbA_{1c}, mmol/mol†	66	74	65	69	70	69
HbA_{1c} ≥7.5% (58 mmol/mol), *n* (% of *n*1)	1,798 (61)	4,953 (74)	4,102 (55)	8,968 (69)	32,611 (72)	53,100 (69)
HbA_{1c} ≥8% (64 mmol/mol), *n* (% of *n*1)	1,364 (47)	4,160 (62)	3,101 (42)	6,974 (54)	26,231 (58)	42,330 (55)
GLP-1RA as third ADD, *n* (% of *n*1)		2,125 (22)	1,532 (12)	1,643 (9)	5,662 (8)	11,230 (9)
INS as third ADD, *n* (% of *n*1)	2,356 (52)		3,338 (27)	5,472 (29)	20,483 (28)	32,447 (27)
TZD as third ADD, *n* (% of *n*1)	241 (5)	688 (7)		1,425 (8)	19,010 (26)	21,472 (18)
DPP-4i as third ADD, *n* (% of *n*1)	481 (11)	2,488 (26)	3,804 (30)		25,216 (34)	32,696 (27)
SU as third ADD, *n* (% of *n*1)	865 (19)	3,090 (32)	3,048 (24)	7,556 (40)		14,844 (12)
SGLT2i as third ADD, *n* (% of *n*1)	521 (12)	938 (10)	138 (1)	2,399 (13)	2,077 (3)	6,095 (5)
Switched to third ADD						
*n*2 (% of *N*)	1,420 (12)	1,002 (3)	6,307 (22)	4,959 (11)	8,204 (6)	22,547 (8)
HbA_{1c}, %*	7.9 (1.6)	8.2 (1.8)	7.8 (1.7)	8.1 (1.7)	8.7 (2)	8.2 (1.8)
HbA_{1c}, mmol/mol†	63	66	62	65	72	66
HbA_{1c} ≥7.5% (58 mmol/mol), *n* (% of *n*2)	470 (54)	377 (60)	1,846 (49)	1,940 (59)	3,380 (68)	8,231 (59)
HbA_{1c} ≥8% (64 mmol/mol), *n* (% of *n*2)	335 (38)	280 (44)	1,290 (34)	1,451 (44)	2,780 (56)	6,286 (45)
GLP-1RA as third ADD, *n* (% of *n*2)		84 (8)	383 (6)	842 (17)	677 (8)	2,065 (9)
INS as third ADD, *n* (% of *n*2)	262 (18)		703 (11)	849 (17)	4,012 (49)	5,931 (26)
TZD as third ADD, *n* (% of *n*2)	61 (4)	48 (5)		273 (6)	510 (6)	924 (4)
DPP-4i as third ADD, *n* (% of *n*2)	488 (34)	269 (27)	2,199 (35)		2,436 (30)	5,561 (25)
SU as third ADD, *n* (% of *n*2)	390 (27)	521 (52)	2,829 (45)	2,456 (50)		6,450 (29)
SGLT2i as third ADD, *n* (% of *n*2)	205 (14)	66 (7)	109 (2)	464 (9)	373 (5)	1,228 (5)

*n*1, number of subcohort 2 patients for each drug class who added a third ADD; *n*2, number of subcohort 2 patients for each drug class who switched to a third ADD. *Mean (SD); †mean; §mean (95% CI). ‡Subcohort 2: those with MET as first-line treatment, who initiated second ADD, with a minimum of 1 year of follow-up post–second drug initiation.

was highest in the SU group (9.0), followed by DPP-4i (3.8) and GLP-1RA (3.2), during >4 years of mean follow-up post–second-line ADD initiation.

We observed that second-line SU users initiate a third ADD marginally sooner compared with incretin users. A study based on EMR data from the U.K. reported the opposite results, with an average of 1.6 and 2.4 years to third ADD initiation in the 3,080 and 15,508 patients treated with MET + DPP-4i and MET + SU, respectively (5).

The proportions of patients who added INS were similar between patients who had a DPP-4i and an SU as the second ADD. However, among those who switched to a third ADD, only 17% of patients in the DPP-4i group switched to INS, compared with almost 50% in the SU group. We also observed that the mean time to INS initiation was significantly shorter for second-line SU users (6.3 years) than in the DPP-4i group (7.1 years). This finding is similar to a study (2015) based on 3,864 matched pairs of patients treated with DPP-4i or SU when added to MET, where Inzucchi et al. (6) reported that those treated with DPP-4i were significantly less likely to initiate INS compared with those treated with SU.

We observed an increasing proportional share of INS as a second-line therapy option over the last 10 years, despite the availability of novel therapies that were found to have similar or better glycemic efficacy in clinical trials. Also, the annual rates of intensification with INS remained similar over the last decade. In a similar study, Lipska et al. (15) observed that the overall rate of severe hypoglycemia did not reduce from 2006 to 2013. This may reflect pressure to achieve glycemic targets rapidly and an increasing recognition that for people with very poor glycemic control, INS may be the only drug likely to achieve targets.

Compared with rates for older ADDs, high discontinuation rates of new therapeutic classes, particularly of DPP-4i, are surprising. The higher cost of these newer drugs may be relevant and may also contribute to the fairly low rates of initiation of these drugs overall. More studies, utilizing additional data sources, are needed to specifically test hypotheses for the differences in initiation, adherence, and persistence between drug classes.

The HbA_{1c} level at pharmacological therapy initiation was found to be 8.2% (66 mmol/mol), with 50% having HbA_{1c} ≥7.5% (58 mmol/mol). The HbA_{1c} levels at first-line ADD initiation were similar across all ADDs, except in those who initiated with INS, whose average HbA_{1c} was 8.9% (74 mmol/mol). Although the mean time to second ADD post–MET initiation was only 8 months, it occurred at a high HbA_{1c} level of 8.4% (68 mmol/mol), with 60% and 48% of patients having HbA_{1c} ≥7.5% (58 mmol/mol) and 8% (64 mmol/mol), respectively. Among those with a minimum of 1 year of follow-up post–second ADD, ~52% intensified with a third ADD at an average HbA_{1c} level of 8.5% (69 mmol/mol). These findings reflect the continued glycemic risk burden in patients with type 2 diabetes (27–30). While the persistent therapeutic inertia (28) and the long-term consequences of therapeutic inertia (27,29) for glycemic control in primary care systems have been evaluated, exploration of the glycemic state at therapy initiation and intensification by ADD classes is scarce. Our study provides a detailed account of the glycemic state in people with type 2 diabetes at therapy initiation and intensifications during a reasonable follow-up period in primary and ambulatory care settings.

The main strength of this study is the availability of data from the patients' medication lists that included prescribed medications within the EMR network and also medication information that could be prescribed outside of the EMR, as well as data on glycemic control and comorbidities. The CEMR database tracks longitudinal treatment adjustments and contains comprehensive clinical information, which is usually not available in claims databases.

The limitations of this study include the nonavailability of complete and reliable data on *1*) medication adherence and side effects, *2*) diet and exercise, *3*) socioeconomic status, and *4*) insurance type. We did not include dosage changes or brands' distribution in our analyses. The findings of this study should be interpreted with caution: EMR data are in general biased toward unhealthy populations and commercially insured individuals, white Caucasians are overrepresented in the CEMR, and the results are subject to limited follow-up.

Less popular ADDs such as MEG, AGI, DOPRA, and amylin were included in our study for multiple reasons: first, to assess utilization data of such medications, as these drugs are usually omitted, and second, to ensure market shares of other drugs are not overestimated. We observed that only 39,549 patients with type 2 diabetes were using SGLT2i during the available follow-up period, which is not surprising, given that they were first approved in 2013.

To conclude, while we have observed significant increase in the use of MET as the first-line therapy over the last 10 years, the second- and third-line therapy intensification choices are highly heterogeneous. While increasing popularity of "new" drugs, especially DPP-4i and SGLT2i, was observed as the second and third drugs choices, SU remain the most popular therapy intensification choice and have a lower discontinuation rate compared with other non-INS ADDs. The proportional share of INS as a second-line therapy choice has also increased significantly over the last decade. Incretin-based therapies were found to delay the need for therapy intensification only marginally compared with other ADDs. Contrary to the guidelines for proactive glycemic management, pharmacological therapy initiation and the intensifications occurred at very high levels of HbA_{1c}, with 48% of patients having HbA_{1c} ≥8.0% (58 mmol/mol) at second-line therapy initiation.

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design. O.M. conducted the data extraction. O.M. and S.K.P. jointly conducted the statistical analyses. F.S. contributed in the interpretation of the results. The first draft of the manuscript was developed by O.M. and S.K.P., and all authors contributed to the finalization of the manuscript. S.K.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. American Diabetes Association. *Standards of Medical Care in Diabetes—2017*: summary of revisions. Diabetes Care 2017;40(Suppl. 1):S4–S5
2. Paul SK, Maggs D, Klein K, Best JH. Dynamic risk factors associated with non-severe hypoglycemia in patients treated with insulin glargine or exenatide once weekly. J Diabetes 2015;7:60–67
3. Paul SK, Shaw JE, Montvida O, Klein K. Weight gain in insulin-treated patients by body mass index category at treatment initiation: new evidence from real-world data in patients with type 2 diabetes. Diabetes Obes Metab 2016;18:1244–1252
4. Waldrop G, Zhong J, Peters M, et al. Incretin-based therapy in type 2 diabetes: an evidence based systematic review and meta-analysis. J Diabetes Complications. 28 August 2016 [Epub ahead of print]. https://doi.org/10.1016/j.jdiacomp.2016.08.018
5. Mamza J, Mehta R, Donnelly R, Idris I. Important differences in the durability of glycaemic response among second-line treatment options when added to metformin in type 2 diabetes: a retrospective cohort study. Ann Med 2016;48:224–234
6. Inzucchi SE, Tunceli K, Qiu Y, et al. Progression to insulin therapy among patients with type 2 diabetes treated with sitagliptin or sulphonylurea plus metformin dual therapy. Diabetes Obes Metab 2015;17:956–964
7. Cohen FJ, Neslusan CA, Conklin JE, Song X. Recent antihyperglycemic prescribing trends for U.S. privately insured patients with type 2 diabetes. Diabetes Care 2003;26:1847–1851
8. Desai NR, Shrank WH, Fischer MA, et al. Patterns of medication initiation in newly diagnosed diabetes mellitus: quality and cost implications. Am J Med 2012;125:302.e1-7
9. Tanne JH. FDA places "black box" warning on antidiabetes drugs. BMJ 2007;334:1237
10. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471
11. Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. N Engl J Med 2010;363:1489–1491
12. Home PD, Pocock SJ, Beck-Nielsen H, et al.; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125–2135
13. Berkowitz SA, Krumme AA, Avorn J, et al. Initial choice of oral glucose-lowering medication for diabetes mellitus: a patient-centered comparative effectiveness study. JAMA Intern Med 2014;174:1955–1962
14. Segal JB, Maruthur NM. Initial therapy for diabetes mellitus. JAMA Intern Med 2014;174:1962–1963
15. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006–2013. Diabetes Care 2017;40:468–475
16. Pantalone KM, Hobbs TM, Wells BJ, et al. Clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. BMJ Open Diabetes Res Care 2015;3:e000093
17. Raebel MA, Xu S, Goodrich GK, et al. Initial antihyperglycemic drug therapy among 241 327 adults with newly identified diabetes from 2005 through 2010: a surveillance, prevention, and management of diabetes mellitus (SUPREME-DM) study. Ann Pharmacother 2013;47:1280–1291
18. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care 2014;37:1367–1374
19. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA, U.S. Department of Health and Human Services, 2014
20. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium, 2015
21. Higgins V, Piercy J, Roughley A, et al. Trends in medication use in patients with type 2 diabetes mellitus: a long-term view of real-world treatment between 2000 and 2015. Diabetes Metab Syndr Obes 2016;9:371–380
22. Crawford AG, Cote C, Couto J, et al. Comparison of GE Centricity Electronic Medical Record database and National Ambulatory Medical Care Survey findings on the prevalence of major conditions in the United States. Popul Health Manag 2010;13:139–150
23. Brixner D, Said Q, Kirkness C, Oberg B, Ben-Joseph R, Oderda G. Assessment of cardiometabolic risk factors in a national primary care electronic health record database. Value Health 2007;10:S29–S36
24. Montvida O, Arandjelović O, Reiner E, Paul SK. Data mining approach to estimate the duration of drug therapy from longitudinal electronic medical records. Open Bioinform J 2017;10:1–15
25. U.S. Food and Drug Administration. FDA approves weight-management drug [article online], 2014. Available from https://wayback.archive-it.org/7993/20170111160832/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm. Accessed 23 December 2014
26. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–1139
27. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100
28. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab 2016;18:401–409
29. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100
30. Montvida O, Klein K, Kumar S, Khunti K, Paul SK. Addition of or switch to insulin therapy in people treated with glucagon-like peptide-1 receptor agonists: a real-world study in 66 583 patients. Diabetes Obes Metab 2017;19:108–117