Journal of Clinical & Translational Endocrinology 22 (2020) 100241

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Cardiovascular disease risk and the time to insulin initiation for Medicaid enrollees with type 2 diabetes

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ARTICLE INFO

Keywords:
Type 2 diabetes
CVD
Insulin initiation

ABSTRACT

Aims: We evaluated the relationship between the timing of insulin initiation and cardiovascular diseases (CVD) risk in Pennsylvania Medicaid enrollees with type 2 diabetes (T2D).
Methods: We included 17,873 enrollees (age 47.4 ± 10.3 years; range 18–64 years) initially treated with non-insulin glucose-lowering agents (GLAs) in 2008–2016. Based on clinical guidelines, we identified early (N = 1,158; 6%; insulin initiation ≤ 6 months after first-line GLAs), in-time (N = 569; 3%; 6–12 months), delayed (N = 2,761; 15%; >12 months), and non-insulin users (N = 13,385; 75%). The Prentice-Williams-Peterson (PWP) models with inverse probability weighting estimated CVD risk across the four groups and the change in risk after insulin initiation.
Results: Regardless of time to insulin initiation, insulin users had higher CVD risks after first-line GLAs than non-insulin users (aHR: early: 2.0 [1.5–2.5], in-time: 1.8 [1.2–2.6], delayed: 1.9 [1.6–2.3]). However, we found only a borderline increase in CVD risk after insulin initiation vs. before in early (aHR: 1.4 [1.1–1.8]) and delayed users (aHR: 1.3 [1.0–1.7]), and no increase in in-time users (aHR: 1.3 [0.9–2.0]).
Conclusions: We observed no gains in CVD benefits from insulin initiation in the early stages of pharmacotherapy possibly because CVD developed before insulin initiation. Additional management of hypertension and dyslipidemia may be important to reduce CVD risk in this young and middle-aged T2D cohort.

Introduction

Insulin initiation occurs after ≥ 2 years of oral glucose-lowering agent (GLA) therapy, on average, among individuals with type 2 diabetes (T2DM) with HbA1c > 8% (64 mmol/mol) in spite of American Diabetes Association (ADA) guidelines that recommend insulin after three months of GLA therapy [1]. Delaying insulin initiation may result in excess myocardial infarction (MI) and other cardiovascular (CVD) events. Prior work has shown that higher HbA1c level and longer duration that HbA1c exceeded 7% were associated with greater CVD risk [2]. Yet studies using real-world data suggest that earlier insulin initiation leads to shorter period of poor glycemic control. A study from Veterans Affairs (VA) reported that patients who initiated insulin after treatment with a single GLA had 10 fewer months of poor glycemic control (HbA1c ≥ 8% [64 mmol/mol]) compared with delayed insulin users with 3 or more GLA trials before insulin use [3]. A study of privately insured patients showed similar benefits for glycemic control associated with earlier insulin initiation [4]. However, evidence remains limited regarding the association between the time to insulin initiation and CVD risk in Medicaid enrollees with type 2 diabetes.

One-fifth of Americans are covered by Medicaid. Medicaid enrollees with type 2 diabetes are younger, have lower incomes, and a higher level of disability and comorbidities than populations included in prior studies [5]. In 2012, 29% of Medicaid enrollees with type 2 diabetes used insulin [6]. The total amount of reimbursement for insulin, including long-acting, short-acting, and rapid-acting insulins, rose by 462% from 2006 to 2014 [7]. One study showed that some cardiovascular diseases including myocardial infarction and stroke was associated with nearly 7 times higher all-cause healthcare cost adjusting for demographic characteristics and comorbidities among Medicaid enrollees

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https://doi.org/10.1016/j.jcte.2020.100241
Received 19 October 2020; Received in revised form 30 October 2020; Accepted 9 November 2020
Available online 11 November 2020

with type 2 diabetes, though these CVD events only impacted 0.7% of this population in 1-year follow-up [5]. To date, no studies have examined the association between the timing of insulin initiation and CVD outcomes among Medicaid enrollees with type 2 diabetes. We address this important gap in the literature using several years of data from one of the largest Medicaid programs in the US. The objective of this study was to evaluate the relationship between the time from first-line GLAs therapy to insulin initiation and the risk of incident and recurrent CVDs in young and middle-aged Medicaid enrollees with type 2 diabetes.

Subjects, materials and methods

Data source and study population

We obtained a Medicaid administrative claims database from the Pennsylvania Department of Human Services (PADHS) to identify this study population. The database includes demographic and enrollment characteristics, pharmacy claims, and ICD9/10-CM diagnosis codes, encounters with procedure information from inpatient and outpatient settings for all Medicaid enrollees in Pennsylvania (PA) from 2007 to 2016. The study sample was limited to 168,594 Medicaid enrollees who had at least one prescription fill for non-insulin GLAs (i.e. metformin, sulfonylurea, thiazolidinedione, inhibitors of dipeptidyl peptidase 4, sodium-glucose co-transporter-2 inhibitor, glucagon-like peptide 1 receptor agonists) [8] from January 1, 2008 through December 31, 2016 (Fig. 1). We excluded Medicaid enrollees age < 18 or > 64 and those who were dually eligible for Medicare for whom Medicare pays for prescription drugs. To identify an incident cohort of new GLA users, we further limited the study cohort to 60,494 enrollees with ≥ 180 days of continuous Medicaid enrollment preceding the index date and without any prescription fills for GLAs before the index date. To exclude those with type 1 or gestational diabetes, we removed enrollees if a) they had no claims with type 2 diabetes diagnostic codes (ICD-9 250 or ICD-10 E11) in any position within 6 months before or after the index date ($N = 16,386$); or b) were women with a birth or a terminated pregnancy within 6 months before or after the index date ($N = 748$). In addition, to allow for long enough follow-up to measure the timing of insulin initiation after first-line GLAs, we excluded enrollees who had < 890 days (2.5 years) of continuous enrollment after their first-line GLAs ($N = 24,582$). During the 2.5 year follow up period, insulin initiators were required to have at least 365 days follow up after starting insulin to allow for adequate measurement of CVD after insulin initiation ($N = 743$). A final cohort of 17,873 Medicaid enrollees with type 2 diabetes was used for analyses (Fig. 1).

Primary independent variables

Time from first-line non-insulin GLAs to insulin initiation, calculated by subtracting the index date from the date of the first prescription fill for insulin, was used to identify four groups: early insulin users (insulin initiation ≤ 6 months after first-line non-insulin GLAs), in-time insulin users (within 6–12 months), delayed insulin users (>12 months), and non-insulin users (never used insulin in the study period). The ADA guidelines recommend insulin as one of treatment options after 3 months of first-line therapy if the glycemic target is not achieved [1]. The guidelines also recommend evaluating treatment intensification every 3–6 months [1]. We used 6 months, which is the maximum recommended interval for medication regimen evaluations and adjustments, as a threshold to determine a wider group of early insulin users. According to guideline recommendations, the 12-month timeframe was selected as a conservative threshold to distinguish between in-time and delayed insulin users.

Outcomes

The primary outcome was the time to incident and recurrent CVD events (acute MI or stroke hospitalization) in the follow-up period from the date of first-line GLAs through the first occurrence of censoring events. Censoring events included the end of enrollment in Pennsylvania Medicaid, gaining dual eligibility for Medicare, all-cause mortality, or the end of follow-up which was set 5 years at maximum for primary analyses.

Acute MI was defined by inpatient claims with a primary discharge diagnosis for nonfatal myocardial infarction (ICD-9 410 or ICD-10 I21-I22). In prior work, this definition had a positive predictive value (PPV) of 90% using an MI registry for case confirmation [9]. Stroke was defined by inpatient claims with a primary discharge diagnosis of ischemic stroke (ICD-9 433.x1, 434.x1, 436 or ICD-10 I63), subarachnoid hemorrhage (ICD-9 430 or ICD-10 I60), intracerebral hemorrhage (ICD-9 431 or ICD-10 I61) or stroke without specifying as hemorrhage or infarction (ICD-10 I64). The PPV for the stroke definition in previous studies was 91% using medical records as the standard [10,11]. Secondary outcomes were the time to incident and recurrent acute MI and

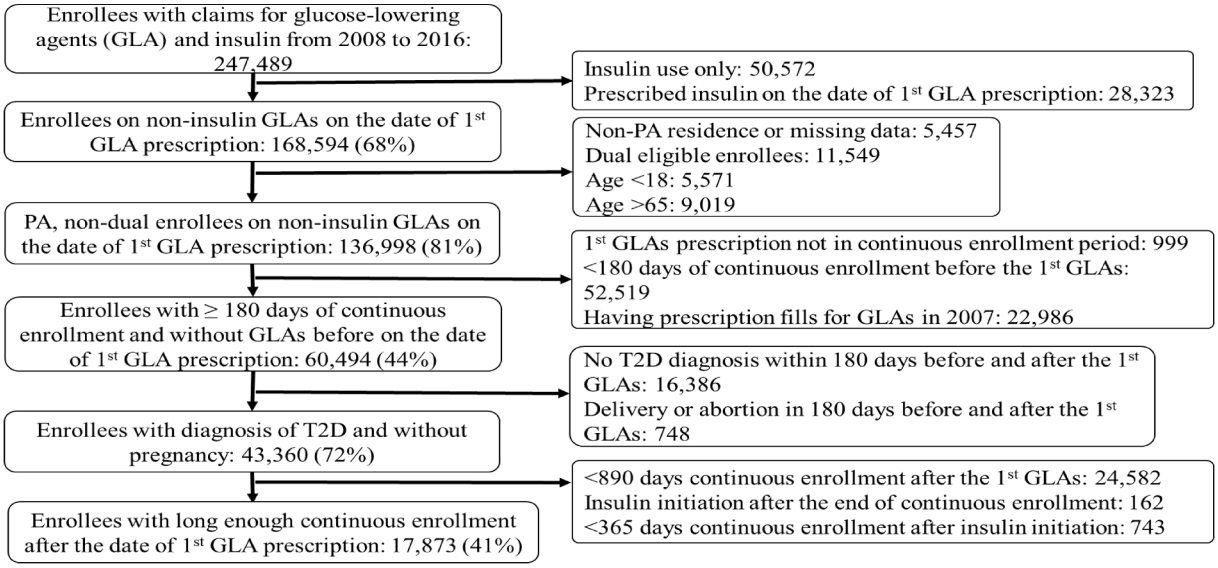

Fig. 1. Flow chart of the eligible patients with type 2 diabetes (T2D) GLA: glucose-lowering agents including metformin, sulfonylurea, thiazolidinedione, inhibitors of dipeptidyl peptidase 4, sodium-glucose co-transporter-2 inhibitor, and glucagon-like peptide 1 receptor agonists. PA: Pennsylvania.

stroke, respectively.

Covariates

To consider potential differences in diabetes severity and health conditions across the four timing of insulin initiation groups, a set of covariates was defined on the date of first-line GLAs that included age, sex, race (White, Black, other), calendar year of the index date, primary enrollment in fee-for-service (as opposed to managed care), and Medicaid eligibility categories, which were grouped into two categories (disabled or chronically ill vs. all others such as Temporary Assistance for Needy Families). Our population effectively excluded the Medicaid expansion group under the Affordable Care Act (ACA) which was implemented in 2015 in PA due to the continuous enrollment criteria. The Area Deprivation Index, an area-based measure of education, income, and occupation status, using the 9-digit ZIP code of residence was included [12]. Several covariates were measured within 1 year before first-line GLAs, including indicators for healthcare utilization (all-cause hospitalization, emergency room [ER] use, and outpatient visits); indicators for certain medication use (anti-hypertensive agents, anticoagulant agents, lipid lowering agents, nitrates, and loop diuretics); indicators for diabetes-related comorbidities and complications (hypertension, obesity, depression, congestive heart failure, nephropathy, neuropathy, retinopathy, cardio/cerebrovascular complications, and metabolic complications) [13]; and a modified Elixhauser comorbidity index excluding the health conditions mentioned above that were included as separate indicators [14] (Supplemental Table S1). These baseline characteristics were used to estimate propensity scores (PS) of insulin users via generalized boosted model (GBM) in which non-insulin users were the counterfactual treatment group [15].

Given that covariates before the index date were accounted in the estimation of PS, two covariates related to GLA prescriptions after the index date were added to the model and removed at $p > 0.1$. The covariates included the number of GLAs from index date to insulin initiation and proportion of days covered (PDC) which was a continuous measure of adherence to first GLA within 6 months after the index date [16].

Statistical analysis

Univariate pairwise comparisons for baseline characteristics within the four groups were conducted using χ^2 tests for categorical variables and ANOVA tests for continuous variables. Inverse probability treatment weighting (IPTW) via propensity scores was applied. This weighting balanced age, sex, race, and other baseline covariates across the four groups. A conditional Cox model proposed by Prentice, Williams, and Peterson (PWP model) was applied in the reweighted population [17]. Given that a number of enrollees had CVD events before insulin initiation, we considered time-to-first event models to be sub-optimal. The PWP model is able to incorporate the time to first CVD events after GLA and also to the subsequent events, in which CVD events occurred either before or after insulin initiation would be considered. We performed PWP models to compare CVD risk from first-line GLAs until the end of follow-up across the four timing of insulin initiation groups. In addition, the PWP model with the time to insulin initiation as a time-dependent predictor (PWP-TDP model) was used to estimate the change of CVD risk after insulin initiation (Fig. 2). In the PWP-TDP model, individuals' status changed from non-insulin users to early, in-time or delayed insulin users, depending on their time to insulin initiation, when they initiated insulin (Fig. 2). Comparing PWP models across the four groups and PWP-TDP models allowed us to consider CVD risk during the period from first-line GLAs to insulin initiation which has been unexamined in prior work on insulin initiation and CVD risk [5]. As a sensitivity analysis to assess whether the duration of follow-up period (i.e. Medicaid enrollment) affected results, we extended the maximum follow-up period from 5 years to 6, 7, 8, or 9 years, respectively. We also performed analyses in the subgroup of enrollees with either ≥ 1, 3, 4, or 5 years, respectively, of continuous enrollment after the index date to shed light on the extent to which our findings were robust to different lengths of continuous enrollment. All analyses were performed using SAS version 9.4.

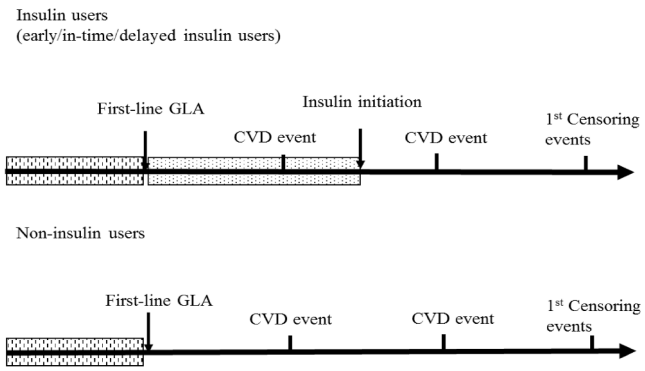

Fig. 2. Timeline of the study The measurement period for baseline covariates was 12 months before first-line GLA (bar with vertical dash). The follow-up period for both insulin users and non-insulin users was from first-line GLA through the first occurrence of censoring events. In Prentice, Williams, and Peterson (PWP) models with the time to insulin initiation as a time-dependent predictor (PWP-TDP model), insulin users' statuses were non-insulin users until they initiated insulin (bar with dots). Insulin users include early insulin users (insulin initiation ≤ 6 months after first-line GLAs), in-time insulin users (within 6–12 months), and delayed insulin users (>12 months). GLA: glucose-lowering agents including metformin, sulfonylurea, thiazolidinedione, inhibitors of dipeptidyl peptidase 4, sodium-glucose co-transporter-2 inhibitor, and glucagon-like peptide 1 receptor agonists. CVD: cardiovascular diseases (acute MI or stroke hospitalization).

Results

In the cohort of 17,873 enrollees with type 2 diabetes, 6% (N = 1,158), 3% (N = 569) and 15% (N = 2,761) were early insulin users (≤6 months), in-time insulin users (6–12 months) and delayed insulin users (>12 months), respectively. The majority (76%, N = 13,385) of enrollees with type 2 diabetes did not use insulin in the study period. In our cohort, there were 95% (N = 17,004) on metformin, 44% (N = 7,856) on sulfonylurea, 8% (N = 1,376) on TZD, 4% (N = 805) on GLP-1 receptor agonists. Before IPTW, four groups had differences in several baseline characteristics. Early insulin users (median [interquartile range, IQR], 4.7 years [3.4–6.2]), in-time insulin users (4.7 years [3.5–6.4]), and non-insulin users (4.5 years [3.5–6.2]) had a shorter median length of Medicaid enrollment after the index event than delayed insulin users (6.1 years, 4.6–7.5). Early (46.0 ± 10.3 years), in-time (44.9 ± 10.8 years), and delayed insulin users (45.6 ± 9.7 years) were slightly younger than non-insulin users (47.4 ± 10.3 years) with all $P < 0.001$. Early insulin users were more likely to be male (40.2% vs 36.8%, $P = 0.02$) and Black (36.2% vs 28.3%, $P < 0.001$) compared to non-insulin users.

Insulin users had more complications than non-insulin users at baseline. Early and in-time insulin users were more likely to have congestive heart failure, cardiovascular complications, nephropathy, and metabolic complications (i.e. diabetic ketoacidosis, hyperglycemic hyperosmolar state, or hypoglycemia) vs. non-insulin users at baseline. Delayed insulin users were comparable to non-insulin users except for a higher prevalence of nephropathy and metabolic complications than non-insulin users. On the other hand, insulin users were less likely to use lipid-lowering agents at baseline than non-insulin users (early: 31.8%; in-time: 32.6%; delayed 37.6% vs. non-insulin users: 43.3%, all $P < 0.001$). After IPTW, all values of standard bias statistics were < 0.2 (Table 1), indicating that age, sex, race, and other observed baseline covariates across the groups obtained balance after IPTW [15].

Table 1
Medicaid enrollees characteristics on the index date or in the year before first-line GLAs and post-treatment covariates, overall and by predictor group.

Characteristics	Overall N = 17873	Early insulin users N = 1158		In-time insulin users N = 569		Delayed insulin users N = 2761		Non-insulin users N = 13385
	Baseline	Baseline	SD	Baseline	SD	Baseline	SD	Baseline
Demographic characteristics								
Age, Mean (SD)	47.4 (10.3)	46.0 (10.3) *	0.05	44.9 (10.8) *	0.01	45.6 (9.7) *	0.01	47.9 (10.3)
Female, N (%)	11,467 (64.2)	692 (59.8) †	0.02	355 (62.4)	0.07	1852 (67.1) †	0.00	8568 (64.0)
Race, N (%)								
Non-Hispanic white	9305 (52.1)	529 (45.7)		303 (53.3)		1423 (51.5)		7050 (52.7)
Non-Hispanic black	5236 (29.3)	419 (36.2) *	−0.05	179 (31.5)	−0.04	849 (30.7)	−0.01	3789 (28.3)
Hispanic	2442 (13.7)	160 (13.8)	0.00	72 (12.7)	−0.03	407 (14.7)	0.00	1803 (13.5)
Others	890 (5.0)	50 (4.3)	−0.01	15 (2.6) †	0.10	82 (3.0) *	0.04	743 (5.6)
FFS, N (%)	4695 (26.3)	316 (27.3)	−0.01	180 (31.6) †	−0.01	941 (34.1) *	−0.02	3258 (24.3)
Disabled, N (%)	13,784 (77.1)	877 (75.7)	0.01	406 (71.4) †	0.00	2169 (78.6)	0.02	10,332 (77.2)
Area deprivation index, Mean (SD)	111.9 (8.1)	111.7 (8.7)	−0.01	111.7 (8.0)	−0.02	112.3 (7.7) †	−0.02	111.9 (8.1)
Length of follow-up								
Mean (SD)	5.1 (1.8)	5.0 (1.8)	–	5.0 (1.8)	–	6.0 (1.8) *	–	4.9 (1.8)
Median (IQR)	4.8 (3.5,6.5)	4.7 (3.4,6.2)	–	4.7 (3.5,6.4)	–	6.1 (4.6,7.5)	–	4.5 (3.4,6.2)
Index year, N (%)								
2008	2603 (14.6)	159 (13.7)	0.01	93 (16.3) †	−0.01	618 (22.4) *	−0.02	1733 (12.9)
2009	2719 (15.2)	160 (13.8)	0.01	85 (14.9)	−0.01	580 (21.0) *	−0.01	1894 (14.2)
2010	2673 (15.0)	146 (12.6)	0.03	81 (14.2)	−0.03	511 (18.5) *	−0.02	1935 (14.5)
2011	2761 (15.4)	200 (17.3)	−0.04	83 (14.6)	0.07	428 (15.5)	−0.02	2050 (15.3)
2012	2748 (15.4)	193 (16.7)	−0.01	95 (16.7)	−0.06	338 (12.2) *	0.01	2122 (15.9)
2013	2907 (16.3)	196 (16.9)	0.00	90 (15.8)	−0.04	225 (8.1) *	0.02	2396 (17.9)
2014	1462 (8.2)	104 (9.0)	0.00	42 (7.4)	0.11	61 (2.2) *	0.06	1255 (9.4)
Health conditions								
Modified Elixhauser index, Mean (SD)	1.4 (1.5)	1.7 (1.8) *	0.00	1.8 (1.8) *	0.03	1.5 (1.6) *	0.01	1.4 (1.5)
Hypertension, N (%)	11,309 (63.3)	676 (58.4) †	0.04	342 (60.1)	0.06	1720(62.3)	0.00	8571 (64.0)
Obesity, N (%)	5908 (33.1)	347 (30.0)	0.00	204 (35.9)	−0.02	902 (32.7)	0.02	4455 (33.3)
Depression, N (%)	5108 (28.6)	358 (30.9)	0.01	182 (32.0)	0.02	832 (30.1)	0.02	3736 (27.9)
Psychoses, N (%)	6406 (35.8)	429 (37.0)	0.01	202 (35.5)	0.06	1034 (37.5)	0.04	4741 (35.4)
Congestive heart failure, N (%)	1038 (5.8)	89 (7.7) †	0.00	52 (9.1) *	−0.02	171 (6.2)	0.01	726 (5.4)
Diabetes complications, N (%)								
Nephropathy	840 (4.7)	70 (6.0) †	−0.01	38 (6.7) †	0.00	154 (5.6) †	0.00	578 (4.3)
Neuropathy	2163 (12.1)	179 (15.5) †	0.00	83 (14.6)	−0.02	330 (12.0)	−0.01	1571 (11.7)
Retinopathy	554 (3.1)	47 (4.1)	0.01	25 (4.4)	−0.01	88 (3.2)	0.00	394 (2.9)
Metabolic complications	186 (1.0)	43 (3.7) *	0.00	11 (1.9) †	0.03	35 (1.3) †	−0.01	97 (0.7)
Peripheral Vascular Disease	1043 (5.8)	91 (7.9) †	0.02	40 (7.0)	−0.01	179 (6.5)	0.00	733 (5.5)
Cardiovascular complications	3138 (17.6)	243 (21.0) †	0.00	122 (21.4) †	0.00	498 (18.0)	−0.01	2275 (17.0)
Cerebrovascular complications	840 (4.7)	64 (5.5)	−0.01	31 (5.4)	0.02	131 (4.7)	0.02	614 (4.6)
Stroke, N (%)	438 (2.5)	39 (3.3)	–	17 (3.0)	–	73 (2.6)	–	309 (2.3)
Acute Myocardial Infarction, N (%)	137 (0.8)	10 (0.9)	–	6 (1.1)	–	19 (0.7)	–	102 (0.8)
Use of medication, N (%)								
Metformin	17,004 (95.1)	1079 (93.2) *	–	533 (93.7) *	–	2652 (96.0) *	–	12,740 (95.2)
Sulfonylurea	7856 (44.0)	598 (51.6) *	–	341 (59.9) *	–	1951 (70.7) *	–	4966 (37.1)
GLP-1 receptor agonists	805 (4.5)	89 (7.7) *	–	56 (9.8) *	–	304 (11.0) *	–	356 (2.7)
TZD	1376 (7.7)	109 (9.4) *	–	58 (10.2) *	–	415 (15.0) *	–	794 (5.9)
Anticoagulants or platelet inhibitors	1353 (7.6)	95 (8.2)	−0.01	48 (8.4)	−0.01	209 (7.6)	0.01	1001 (7.5)
Nitrates	690 (3.9)	46 (4.0)	−0.03	24 (4.2)	0.00	111 (4.0)	0.00	509 (3.8)
Loop Diuretics	1867 (10.4)	116 (10.0)	0.02	63 (11.1)	0.02	340 (12.3) *	−0.01	1348 (10.1)
Adherence to medication, N (%)								
Use of Anti-hypertensive medications								
No	10,116 (56.6)	670 (57.9)	0.01	339 (59.6)	0.04	1633 (59.1)	0.03	7474 (55.8)
Yes, with PDC < 80%	4904 (27.4)	359 (31.0)	–	152 (26.7)	–	760 (27.5)	–	3633 (27.1)
Yes, with PDC ≥ 80%	2853 (16.0)	129 (11.1) ‡	–	78 (13.7)	–	368 (13.3) ‡	–	2278 (17.0)
Use of Statin and other lipid lowering agents								
No	10,494 (58.7)	790 (68.2)	0.04	384 (67.5)	0.06	1721 (62.3)	0.03	7599 (56.8)
Yes, with PDC < 80%	5510 (30.8)	314 (27.1) ‡	–	150 (26.4) ‡	–	835 (30.2) §	–	4211 (31.5)
Yes, with PDC ≥ 80%	1869 (10.5)	54 (4.7) ‡	–	35 (6.2) ‡	–	205 (7.4) ‡	–	1575 (11.8)
Healthcare utilization								
All-cause hospitalization, N (%)	4235 (23.7)	387 (33.4) *	–	204 (35.9) *	–	779 (28.2) *	–	2865 (21.4)
Number of hospitalization episodes								
Mean (SD)	0.4 (1.0)	0.6 (1.2) *	0.02	0.7 (1.7) *	0.05	0.5 (1.2) *	0.00	0.3 (0.9)
Median (IQR)	0.0 (0.0,0.0)	0.0 (0.0,1.0)	–	0.0 (0.0,1.0)	–	0.0 (0.0,1.0)	–	0.0 (0.0,0.0)
All-cause ER visits, N (%)	9022 (50.5)	659 (56.9) *	–	337 (59.2) *	–	1546 (56.0) *	–	6480 (48.4)
Number of ER visits								
Mean (SD)	1.5 (3.9)	1.9 (4.3) *	0.00	2.0 (3.7) †	0.03	1.8 (3.4) *	0.02	1.4 (3.9)
Median (IQR)	1.0 (0.0,2.0)	1.0 (0.0,2.0)	–	1.0 (0.0,2.0)	–	1.0 (0.0,2.0)	–	0.0 (0.0,2.0)
All-cause outpatient visits, N (%)	17,024 (95.2)	1045 (90.2) *	–	526 (92.4) *	–	2590 (93.8) *	–	12,863 (96.1)
Number of outpatient visits								
Mean (SD)	16.0 (21.7)	12.9 (18.7) *	–	16.5 (31.4)	–	15.6 (19.1)	–	16.4 (21.9)
Median (IQR)	9.0 (4.0,20.0)	7.0 (2.0,16.0)	–	8.0 (3.0,19.0)	–	10.0 (4.0,20.0)	–	10.0 (4.0,20.0)
Post-treatment covariates								

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Overall N = 17873	Early insulin users N = 1158		In-time insulin users N = 569		Delayed insulin users N = 2761		Non-insulin users N = 13385
	Baseline	Baseline	SD	Baseline	SD	Baseline	SD	Baseline
Number of non-insulin GLAs¶ in 6 months after index date								
Mean (SD)	1.3 (0.5)	1.5 (0.7) *	–	1.5 (0.6) *	–	1.4 (0.6) *	–	1.2 (0.4)
Median (IQR)	1.0 (1.0,1.0)	1.0 (1.0,2.0)	–	1.0 (1.0,2.0)	–	1.0 (1.0,2.0)	–	1.0 (1.0,1.0)
Number of non-insulin GLAs¶ from index date to insulin initiation								
Mean (SD)	1.7 (0.9)	1.4 (0.6) †	–	1.7 (0.7) †	–	2.2 (1.0)	–	1.6 (0.9)
Median (IQR)	1.0 (1.0,2.0)	1.0 (1.0,2.0)	–	2.0 (1.0,2.0)	–	2(1.0,3.0)	–	1.0 (1.0,2.0)

Early insulin users: insulin initiation ≤ 6 months after first-line non-insulin GLAs)
In-time insulin users: insulin initiation within 6–12 months
Delayed insulin users: insulin initiation > 12 months
Non-insulin users: never used insulin in the study period
IQR: interquartile range
SD in the header row: standard differences in mean compared with non-insulin users
FFS: fee-for-service
ER: emergency room
PDC: proportion of days covered
* p-value < 0.001, non-insulin users as reference
† p-value < 0.05, non-insulin users as reference
‡ p-value < 0.001, non-insulin users without use of anti-hypertensives/lipid lowering medications, respectively, as reference
§ p-value < 0.05, non-insulin users without use of anti-hypertensives/lipid lowering medications, respectively, as reference
|| Modified Elixhauser Comorbidity Index evaluated 22 comorbidities, excluding hypertension, obesity, depression, psychoses, congestive heart failure, diabetes and diabetes related complications which are shown separately;
¶ Non-insulin GLAs included Biguanides, Dopamine-2 Agonists, DPP-4 inhibitors, Meglitinides, SGLT2 Inhibitors, Sulfonylureas, TZDs, GLP-1 Receptor Agonists, Amylin Analogs and combined therapy

The crude incident CVD rates after first-line GLAs were 11.1 per 1000 person-years for early insulin users, 10.1 for in-time insulin users, 12.1 for delayed insulin users, and 6.1 for non-insulin users. All three groups of insulin users had a higher CVD risk after first-line GLAs compared to non-insulin users (early insulin users: aHR, 2.0 [1.5–2.5]; in-time insulin users: aHR, 1.8 [1.2–2.6]; delayed insulin users: aHR, 1.9 [1.6–2.3]; Table 2). In the PWP-TDP models, both early and delayed insulin users had slightly higher CVD risks after insulin initiation compared to before (early insulin users: aHR, 1.4 [1.1–1.8]; delayed insulin users: aHR, 1.3 [1.0–1.7]). In-time insulin users did not have an increased CVD risk after insulin initiation (aHR, 1.3 [0.9–2.0]). The results of sensitivity analyses with varied durations of follow-up periods (i.e. 6, 7, 8, and 9 years, respectively) were consistent with the primary analyses. Sensitivity analyses in the subgroup of enrollees with continuous enrollment for ≥ 3, ≥ 4, and ≥ 5 years, respectively, after the index date had a similar result to the primary analyses. Relaxing the inclusion criterion relating to continuous enrollment from ≥ 2.5 years to ≥ 1 year did not substantially alter findings (Supplemental Table S2).

In the secondary analyses with stroke as the outcome, the results were consistent with the primary analyses for CVD events (acute MI or stroke). The risk of incident and recurrent acute MI from first-line GLAs until the end of follow-up was 1.9 times (95% CI, 1.3–2.7) higher in early insulin users and 2.0 times (95% CI, 1.6–2.6) higher in delayed insulin users than non-insulin users. In-time insulin users had a similar MI risk from first-line GLAs until the end of follow-up compared to non-insulin users (aHR, 1.6 [0.9–2.8]). In the PWP-TDP models, the risk of acute MI risk after vs. before insulin initiation in delayed insulin users increased by 60% (aHR, 1.6 [1.2–2.2]; adjusted P-value, 0.03). In early

Table 2
Adjusted hazard ratios (95% confidence interval [CI]) for recurrent CVD events after first-line GLAs comparing three insulin user groups with non-users using an Prentice, Williams, and Peterson (PWP) model.

	No. enrollees with events	No. events	Model 1 HR (95%CI)	Adjusted P-value	Model 2 HR (95%CI)	Adjusted P-value
CVD (i.e. Acute MI or stroke) in people with >=2.5 year enrollment						
Early insulin users	53	75	1.95 (1.52,2.51)	<0.01	1.35 (1.04,1.75)	0.08
In-time insulin users	24	31	1.76 (1.20,2.57)	<0.01	1.34 (0.89,2.01)	0.33
Delayed insulin users	152	185	1.88 (1.57,2.25)	<0.01	1.33 (1.04,1.71)	0.08
Non-insulin users	337	414				
Acute MI in people with >=2.5 year enrollment						
Early insulin users	35	44	1.87 (1.31,2.66)	<0.01	1.20 (0.83,1.73)	0.49
In-time insulin users	12	14	1.61 (0.92,2.82)	0.19	1.35 (0.76,2.39)	0.49
Delayed insulin users	89	105	2.03 (1.59,2.58)	<0.01	1.59 (1.15,2.19)	0.03
Non-insulin users	183	216				
Stroke in people with >=2.5 year enrollment						
Early insulin users	23	31	2.05 (1.43,2.94)	<0.01	1.51 (1.05,2.16)	0.15
In-time insulin users	15	17	1.91 (1.13,3.22)	0.03	1.34 (0.74,2.41)	0.66
Delayed insulin users	65	80	1.77 (1.36,2.31)	<0.01	1.09 (0.73,1.63)	0.73
Non-insulin users	162	198				

*Adjusted P-value was the corrected p-value with false discovery rate controlling adjustments for multiple comparisons. No difference was detected among three groups of insulin users.
All models adjusted for inverse probability treatment weighting (IPTW) accounting for differences in characteristics and health conditions at baseline, as well as adjusted for the proportion of days covered (PDC) measured within 6 months after the first-line GLA therapy (index date)
Model 1- PWP model to compare CVD risk from first-line GLAs until the end of follow-up across the four timing insulin initiation groups
Model 2- PWP model with the time to insulin initiation as a time-dependent predictor (PWP-TDP model)

and in-time insulin users, no difference was found in acute MI risk after vs. before insulin initiation.

Discussion

This study had three key findings regarding young and middle-aged Medicaid enrollees with type 2 diabetes in Pennsylvania. First, 76% of Medicaid enrollees with type 2 diabetes (N = 13,385) did not initiate insulin in the average follow-up period of 5.1 years from first-line GLAs. Among insulin users, the average time from the first-line GLAs to insulin initiation was 23 months. Second, insulin users regardless of time to insulin initiation had a higher CVD risk after first-line GLAs compared to non-insulin users, after controlling for several baseline demographic factors, comorbidities, and complications. Third, the CVD risk in insulin users did not significantly change after insulin initiation vs. before. To our knowledge, this is the first study to describe the time from first-line therapy to insulin initiation and lack of change in CVD risk in a low-income young and middle-aged Medicaid type 2 diabetes population with a high level of disability, and comorbid mental health and physical health conditions.

Consistent with prior observational studies [18–20], in our Medicaid cohort, insulin users were found to have a higher prevalence of complications at baseline than non-insulin users. We employed IPTW analyses to balance the prevalence of comorbidities, complications and other observable features before first-line GLA. The strength of the association of insulin initiation and increased CVD risk persisted even after IPTW. However, our ability to test this hypothesis is limited by the fact that we are unable to adjust for clinical variables not available in administrative data (e.g., HbA1c levels, lipid profiles, blood pressure, body weight, duration of diabetes, and smoking status). Data from RCTs such as the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial [21] suggest that the observed increased CVD risk among insulin users in our real-world study may be attributed to having unmeasured CVD risk factors or comorbidities before first-line GLAs.

Our finding of no difference in CVD risk between early, in-time and delayed insulin users differed from previous studies. Clinical trials show that early insulin initiation preserves pancreatic beta-cell function, thus helping maintain glycemic control, prevent long-term microvascular complications, and slightly reduce the risk of non-fatal MI [22,23]. Due to lack of HbA1c levels in claims data, the time when enrollees' glycemic levels were > 8% (64 mmol/mol) could not be observed. Therefore, our study measured the timing of insulin initiation relative to the course of pharmacotherapy vs. timing of the progression of disease. Our study compared PWP models across the four groups based on the timing of insulin initiation and PWP-TDP models to distinguish CVD risk after insulin initiation from CVD risk after first-line GLAs. The PWP models for four groups showed after their first-line GLAs, insulin users had a significant higher CVD risk vs. non-insulin users; while the PWP-TDP models showed that CVD risk did not significantly increase after insulin initiation. The results from these two models suggested insulin users had CVD events occurred during the period from first-line GLAs to insulin initiation, regardless of timing of insulin initiation. The results from these two models suggested CVD events had already occurred among Medicaid enrollees on insulin during the period from first-line GLAs to insulin initiation, regardless of timing of insulin initiation. The irreversible formation of atherosclerotic plaque and CVDs development before insulin initiation even at the early course of pharmacotherapy may limit the role of improved glycemic control for altering or impeding the process of atherogenesis [24]. Our findings indicate that clinicians may be initiating insulin reactively to slow down the progression of complications rather than proactively to prevent the occurrence of complications [25].

The lack of CVD benefit of early insulin initiation may also be explained by inadequate management for other CVD risk factors such as smoking, dyslipidemia and hypertension. With elevated total cholesterol, systolic blood pressure and cigarette use, the absolute risk of CVD deaths increases more steeply in adults with diabetes vs. without diabetes, indicating the importance of CVD risk factor management for those with diabetes [26]. Clinical trials further supported that interventions targeting at blood pressure and cholesterol levels reduced CVD risk in middle-aged adults with type 2 diabetes [27]. The Framingham Heart Study showed two thirds of middle-aged adults did not meet their goals for blood pressure or cholesterol levels [28,29]. Only 40% of Medicaid enrollees with type 2 diabetes used statin and other lipid lowering agents, which is lower than 52% in adults with diabetes in a nationally representative survey [30] although the mean age in that study (60 years) was higher than in our study (47 years). Our study found a much lower proportions of patients with high adherence (i.e. proportion of days covered by medications ≥ 80%) to anti-hypertensive medications or lipid-lowering agents at baseline compared to prior work in diabetes populations with commercial or Medicare insurance for anti-hypertensives (16% vs. 46%) and lipid-lowering agents (10% vs. 38%) [31]. Improving management for CVD risk factors in young and middle-aged Medicaid enrollees with type 2 diabetes may be needed for CVD prevention, particularly since our results indicate that insulin initiation did not decrease CVD risk.

The main strength of our study is examination of CVD risk both before and after insulin initiation, which had not been addressed in previous studies. The relatively large sample size and the average follow-up period of 5.1 years from first-line GLAs enabled us to include a substantial number of CVD events for analyses. In addition, our Medicaid database, obtained directly from the state of PA, captures medication and healthcare utilization from enrollees in managed care plans, which is not available in the Medicaid databases from the Centers for Medicare and Medicaid Services (CMS). The comprehensive reporting system for encounter data in the PADHS guarantees a reliable and valid measure of utilization from managed care. Finally, we applied a machine learning approach (i.e. generalized boosting methods) to estimate propensity scores for three groups of insulin users. This iterative estimation procedure can capture complex and nonlinear relationships between predictors and baseline variables without over-fitting the data and achieve best balance between four groups avoiding extreme PS [15]. Large claims databases and novel statistical methods enabled an investigation of the effect of insulin initiation in Medicaid population who are a young and middle-aged population in poor health that have rarely been included in the existing literature.

The major limitation is that some potential confounders were not available in our claims data. In addition, we did not have data to evaluate CVD mortality as an outcome, which may have underestimated total CVD risk. However, the relatively low rate of CVD mortality in middle-age adults may not significantly impact the results [32]. A maximum of five years of follow up was considered for the primary analyses to ensure that all four groups were assessed in the same time horizon; though delayed insulin users had a significantly longer period of continuous enrollment in Medicaid compared to other groups. Those in the delayed insulin group may have had better glycemic control on non-insulin GLAs, though we could not address this since the timing of switching to insulin depended on HbA1c which is unavailable in our data. Due to infrequent use of SGLT2 inhibitors and GLP-1 receptor agonists in our study population in 2007–2016, our study did not thoroughly examine the impact of these two drugs with respect to the treatment for CVD among patients with diabetes. Our study may not have enough power to detect significant difference in CVD risk between in-time insulin users, the smallest group, vs. non-insulin users. Finally, our findings from the Medicaid population in Pennsylvania may not generalize to other states due to variations in demographic distributions, prevalence of diabetes, cost containment policies to limit the use of insulin as well as timelines to implement Medicaid expansion under the Affordable Care Act (ACA) [33–35]. For instance, in Pennsylvania, human and analog basal or bolus insulin are able to be prescribed without prior authorization, while in Massachusetts and Maine, more restrictions exist in prescribing some bolus formulations and insulin

pens [34,35]. Additionally, our results may not be applicable in privately insured populations in which the proportions of racial minorities and women are different than our Medicaid enrollees [36]. The findings in our research should be reevaluated in populations in other states, settings or with different demographic characteristics in the future.

Our findings indicate even with insulin initiation in the early course of type 2 diabetes pharmacotherapy, young and middle-aged PA Medicaid enrollees may not be protected from future CVD risk. Potential explanations include poor CVD risk factor management at middle age or that CVD was pre-existing or concurrent to the diagnosis of type 2 diabetes and/or insulin initiation. Screening and treatments for other CVD risk factors such as blood pressure and blood lipid levels may be important to reduce incident CVD in this young and middle-aged Medicaid population with type 2 diabetes.

Author contributions

LX wrote the manuscript and analyzed study data. LX, ES, RB, JZ, TC and JD contributed to the study concept and design. LX, ES, RB and JD interpreted study data. ES, RB, JZ, TC, DK and JD provided critical review and edits to the manuscript and gave final approval before submission. J.D. 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. The authors thank Jie Li and Aiju Men for expert programming.

Funding

This study and medical writing for this manuscript were funded by the National Heart Lung and Blood institute (NHLBI) through a research grant (R01HL119246). NHLBI had no role in the design of the study, the writing of the manuscript, or in the collection, analysis, or interpretation of the data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2020.100241.

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