Cardiovascular Risk Factor Burden in People With Incident Type 2 Diabetes in the U.S. Receiving Antidiabetic and Cardioprotective Therapies

Olga Montvida, Xiaoling Cai, and Sanjoy K. Paul

Diabetes Care 2019;42:644–650 | https://doi.org/10.2337/dc18-1865

OBJECTIVE

Individualized treatment of patients with diabetes requires detailed evaluation of risk factor dynamics at the population level. This study evaluated the persistent glycemic and cardiovascular (CV) risk factor burden over 2 years after treatment intensification (TI).

RESEARCH DESIGN AND METHODS

From U.S. Centricity Electronic Medical Records, 276,884 patients with incident type 2 diabetes who intensified metformin were selected. Systolic blood pressure (SBP) ≥130/140 mmHg and LDL ≥70/100 mg/dL were defined as uncontrolled for those with/without a history of CV disease at TI. Triglycerides ≥150 mg/dL and HbA_{1c} ≥7.5% (58 mmol/mol) were defined as uncontrolled. Longitudinal measures over 2 years after TI were used to define risk factor burden.

RESULTS

With 3.7 years' mean follow-up, patients were 59 years; 70% were obese; 22% had a history of CV disease; 60, 30, 50, and 48% had uncontrolled HbA_{1c}, SBP, LDL, and triglycerides, respectively, at TI; and 81% and 69% were receiving antihypertensive and lipid-modifying therapies, respectively. The proportion of patients with consistently uncontrolled HbA_{1c} increased from 31% in 2005 to 41% in 2014. Among those on lipid-modifying drugs, 41% and 37% had consistently high LDL and triglycerides over 2 years, respectively. Being on antihypertensive therapies, 29% had consistently uncontrolled SBP. Among patients receiving cardioprotective therapies, 63% failed to achieve control in HbA_{1c} + LDL, 57% in HbA_{1c} + SBP, 55% in LDL + SBP, and 63% in HbA_{1c} + triglycerides over 2 years after TI.

CONCLUSIONS

Among patients on multiple therapies for risk factor control, more than one-third had uncontrolled HbA_{1c}, lipid, and SBP levels, and more than one-half had two CV risk factors that were simultaneously uncontrolled after TI.

Cardiovascular disease (CVD) in patients with type 2 diabetes has been much in focus during the last decade and remains so to date, being the most common reason for death and comorbidities among patients with diabetes (1,2). The efficient management of these patients requires a multifaceted approach to holistically

Melbourne EpiCentre, University of Melbourne and Melbourne Health, Melbourne, Australia

Corresponding author: Sanjoy K. Paul, sanjoy.paul@unimelb.edu.au

Received 5 September 2018 and accepted 27 December 2018

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1865/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

control for hyperglycemia and for abnormal levels of cardiovascular (CV) risk factors such as blood pressure, body weight, and lipids (3,4). In this context, a population-level assessment of those who consistently fail to control risk factors would help our understanding of whether increasing evidence of early control benefits and introduction of newer classes of antidiabetic drugs (ADDs) has helped to improve population health during the last decade. A recent review by Khunti et al. (5) discussed current evidence of early control of glucose, lipids, and blood pressure on CV benefits.

Although American and international guidelines elaborate the importance of cardiometabolic risk factor control in patients with type 2 diabetes, the U.S. survey data suggest that population-level control has not improved during the last decade (6–8). Using data from U.S. National Health and Nutrition Examination Survey (NHANES), Carls et al. (8) reported that 57% of patients with diabetes during 2003–2006 achieved HbA_{1c} <7% (53 mmol/mol), whereas only 51% did so in 2011–2014. Similarly, using data for privately insured and Medicare Advantage patients with type 2 diabetes, Lipska et al. (7) reported a marginally declining proportion of patients with HbA_{1c} <7% (53 mmol/mol) from 56% in 2006 to 54% in 2013. Ali et al. (6) reported that only 14% of patients with diabetes had simultaneous control of glucose, blood pressure, cholesterol, and nonsmoking status during 1999–2010 in the U.S. Another study of 530,747 patients from the Diabetes Collaborative Registry reported that 83% of patients have hypertension and 81% have hyperlipidemia (3).

A significant portion of patients with type 2 diabetes eventually intensify first-line metformin apart from using multiple cardioprotective medications; nonetheless, poor cardiometabolic risk factor control is common in these patients. A number of studies based on survey data and real-world electronic medical records (EMRs) have evaluated the glycemic risk factor burden (6,9) and the existence of therapeutic inertia (10,11) and its implication at the population level (12). However, we are not aware of any study based on real-world data that has holistically explored the patterns of glycemic and CV risk factor control simultaneously after therapy intensification (TI) at the population level.

Among patients with type 2 diabetes receiving antidiabetic and cardioprotective therapies for risk factor control, identified from U.S. primary and secondary ambulatory care systems' EMRs, the aims of this retrospective longitudinal cohort study were to provide a holistic evaluation of the *1*) patterns of failure in HbA_{1c}, systolic blood pressure (SBP), LDL cholesterol, and triglyceride control over 2 years after therapy initiation, and *2*) the annual trend of the burden of these risk factors from 2005 to 2016.

RESEARCH DESIGN AND METHODS

Data Source

Centricity Electronic Medical Records (CEMR) is a centralized EMR solution that incorporates patient-level data from participating independent physician practices, academic medical centers, hospitals, and large integrated delivery networks covering all states of the U.S. CEMR partners contribute de-identified patient-level data to enable quality improvement, benchmarking, and population-based medical research. With an average follow-up of 4.5 years, the CEMR database covers more than 35,000 health care providers, where ~70% are primary care providers. Patients in the database are generally representative of the U.S. population, and among those who were active in the CEMR during 2015 and were older than 18 years, 11.6% were identified to have any type of diabetes. This estimate stands very close to the *U.S. National Diabetes Statistics Report* that estimated 12.2% of the adult population had diabetes in 2015 (13). The database has been extensively used for academic research worldwide (14–16).

Longitudinal EMRs were available from 1995 until April 2016 for more than 34 million individuals, with comprehensive patient-level information on medications and demographic, anthropometric, clinical, and laboratory variables.

Study Design

The main study cohort included patients with *1*) age at type 2 diabetes diagnosis ≥18 and <80 years, *2*) diagnosis date on or after 1 January 2005 and strictly after the first registered activity in the EMR database, *3*) initiated antidiabetic therapy with metformin, *4*) initiated second-line ADD and continued it for at least 3 months, *5*) available HbA_{1c}, SBP, LDL, or triglycerides measured at second-line ADD initiation (baseline), and *6*) follow-up from baseline of at least 6 months. Additional restrictions on the follow-up were applied: ≥12 months (subcohort 1) and ≥24 months (subcohort 2). We recently described a robust methodology for extraction and assessment of longitudinal patient-level medication data from the CEMRs (17) and reported a detailed account of ADD use in the U.S. population, based on the CEMR (18).

HbA_{1c} measures at baseline and 6, 12, 18, and 24 months were obtained as the nearest measure within 3 months either side of the time point. Baseline and longitudinal body weight, SBP, and lipids were calculated as the average of available measures within 3 months either side of the time point.

The presence of comorbidities before baseline was assessed by relevant disease identification codes (ICD-9, ICD-10, or SNOMED Clinical Terms). CVD was defined as ischemic heart disease, peripheral vascular/artery disease, heart failure, or stroke. The Charlson Comorbidity Index was defined and calculated following the algorithm described by Quan et al. (19). Lipid-modifying agents included all U.S. Food and Drug Administration–approved drugs with the highest Anatomical Therapeutic Chemical classification code of C10. Antihypertensive drugs were defined by the Anatomical Therapeutic Chemical codes C02–C04 and C07–C09 (includes diuretics and vasodilators).

SBP ≥130/140 mmHg for those with/without CVD history at baseline was defined as uncontrolled. Similarly, LDL ≥70/100 mg/dL for those with/without CVD history at baseline was defined as uncontrolled. Triglycerides ≥150 mg/dL and HbA_{1c} ≥7.5% (58 mmol/mol) were defined as uncontrolled (4,20–22).

Statistical Methods

Baseline characteristics are summarized as number (%), mean (SD), or median (first quartile, third quartile). The main cohort, subcohort 1, and subcohort 2 were used for the analyses at 6, 12, and 24 months, respectively. Patients with no record of CVD on or before second-line ADD initiation, but who

developed it later, were analyzed in the "no history of CVD" group.

With the condition of at least two nonmissing follow-up data over 24 months and complete data at baseline, the missing HbA_{1c} and CV risk factor data were imputed using a Markov Chain Monte Carlo method adjusting for age, diabetes duration, and usage of concomitant ADDs (23).

Longitudinal failure to control risk factors (individual and pairwise) was summarized as the proportion (95% CI) at 6, 12, and 24 months after baseline and was calculated irrespective of baseline control status. Failure to control risk factors among those who were uncontrolled at baseline was also summarized as the proportion (95% CI) at 6, 12, and 24 months of baseline, where only those uncontrolled patients with baseline $HbA_{1c} \leq 9\%$ (75 mmol/mol) contributed to calculations due to clinical considerations. For all analyses, failure to control LDL and triglycerides at 6, 12, and 24 months was calculated in those who were using a lipid-modifying drug before 6, 12, and 24 months of baseline, respectively. Similarly, failure to control SBP was calculated only in those who were using an antihypertensive drug before 6, 12, and 24 months of baseline.

The 2-year risk factor burden was defined as uncontrolled measures (at 6 months OR at 12 months) AND (at 18 months OR at 24 months) for patients in subcohort 2. The 2-year burden for lipids/blood pressure was calculated among those who were using a lipid-modifying/antihypertensive drug during the evaluation period.

Table 1—Cohort characteristics at the time of second-line ADD initiation

	All *N* = 276,884	No history of CVD *N* = 276,884	History of CVD *N* = 60,317
Age, years*	59 (12)	57 (12)	64 (9)
Male†	136,918 (49)	99,907 (46)	37,011 (61)
White†	194,758 (70)	149,180 (69)	45,578 (76)
Black†	32,671 (12)	27,274 (13)	5,397 (9)
Time from metformin initiation, months*	7.5 (15.7)	7.1 (15.2)	9.0 (17.4)
Follow-up, years*	3.7 (2.4)	3.7 (2.5)	3.6 (2.4)
Follow-up ≥12 months†	247,223 (89)	193,092 (89)	54,131 (90)
Follow-up ≥24 months†	191,883 (69)	149,833 (69)	42,050 (70)
Therapy duration, months*	33 (25)	33 (25)	33 (24)
HbA_{1c}, %*	8.4 (1.9)	8.5 (1.9)	8.1 (1.7)
HbA_{1c}, mmol/mol	68	69	65
HbA_{1c} ≥7.5% (58 mmol/mol)†	102,624 (60)	84,835 (61)	17,789 (54)
Weight, kg*	99 (25)	100 (25)	97 (23)
BMI, kg/m^2*	35 (8)	35 (8)	33 (7)
BMI <25 kg/m^2†	18,819 (7)	13,735 (7)	5,084 (9)
BMI ≥25 and <30 kg/m^2†	60,575 (23)	44,963 (22)	15,612 (27)
BMI ≥30 kg/m^2†	187,936 (70)	150,067 (72)	37,869 (65)
SBP, mmHg*	131 (15)	131 (15)	130 (16)
Uncontrolled SBP†§	82,837 (30)	53,168 (25)	29,669 (50)
DBP, mmHg*	77 (9)	78 (9)	75 (9)
LDL, mg/dL*	97 (35)	100 (35)	87 (34)
Uncontrolled LDL†‖	71,424 (50)	51,077 (46)	20,347 (67)
HDL, mg/dL*	43 (12)	44 (12)	42 (12)
Triglycerides, mg/dL‡	147 (107, 197)	148 (107, 198)	146 (107, 195)
Triglycerides ≥150 mg/dL†	54,640 (48)	43,240 (49)	11,400 (48)
Chronic kidney disease†	9,602 (3)	5,793 (3)	3,809 (6)
Cancer†	13,750 (5)	9,951 (5)	3,799 (6)
Depression†	38,444 (14)	29,996 (14)	8,448 (14)
Charlson Comorbidity Index*	1.6 (1.1)	1.4 (0.9)	2.4 (1.4)
Any lipid-modifying drug†	188,272 (68)	137,391 (63)	50,881 (84)
Statin†	168,485 (61)	121,287 (56)	47,198 (78)
Blood pressure–lowering drug†	224,086 (81)	167,177 (77)	56,909 (94)

*Mean (SD). †*n* (%). ‡Median (first quartile, third quartile). §Uncontrolled SBP: ≥130/140 mmHg for those with/without history of CVD at the time of second-line ADD initiation. ‖Uncontrolled LDL: ≥70/100 mg/dL for those with/without history of CVD at the time of second-line ADD initiation.

RESULTS

From 2,624,954 identified patients with type 2 diabetes, 276,884 met inclusion criteria (Supplementary Fig. 1 and Table 1). With a mean follow-up of 3.7 years, 89% of the cohort had at least 1 year of follow-up. In the cohort, 187,936 patients (70%) were obese, and 60,317 (22%) had a history of CVD on or before the baseline. Those with a history of CVD were older (mean 64 years) and more likely to be male (61%) than those without a history of CVD (mean 57 years; 46% male). Among those with/without a history of CVD, 8,130 (13%)/10,353 (5%) had a record of CVD within 6 months of baseline. With a mean (SD) HbA_{1c} of 8.4% (1.9) (68 mmol/mol) at the time of the second ADD initiation, 54/61% of patients with/without history of CVD had $HbA_{1c} \geq 7.5\%$ (58 mmol/mol), respectively. With a mean (SD) LDL of 97 (35) mg/dL, 67% of those with a CVD history had LDL ≥70 mg/dL, and 46% of those without a CVD history had LDL ≥100 mg/dL. Approximately 48% had baseline triglycerides ≥150 mg/dL.

In subcohort 1, among those with/without a history of CVD, 90/74% were using a lipid-modifying drug before or within 1 year of baseline (data not shown). With a mean (SD) SBP of 131 (15) mmHg, 50% of those with a history of CVD had SBP ≥130 mmHg, whereas 25% of those without a CVD history had SBP ≥140 mmHg. In subcohort 1, among those with/without history of CVD, 97/84% were using an antihypertensive drug before or within 1 year of baseline (data not shown).

Individual Risk Factor Failure

Irrespective of baseline control, 37, 39, and 42% of patients failed to achieve $HbA_{1c} < 7.5\%$ (58 mmol/mol) at 6, 12, and 24 months after intensification with a second-line ADD (Table 2). The proportions of those who failed to control HbA_{1c} were lower for those with a history of CVD at baseline (32–38%) compared with those without a history of CVD at baseline (38–42%, data not shown). In the cohort of patients without a history of CVD at baseline but who developed CVD during follow-up, these proportions were marginally higher (34–39%).

Table 2—Proportions (95% CI) of those who failed to control* individual risk factors and who failed to control two risk factors simultaneously at 6, 12, and 24 months after second-line ADD initiation

	6 months	12 months	24 months
Individual failure			
HbA_{1c}	37 (36–37)	39 (39–39)	42 (41–42)
LDL	43 (43–43)	43 (43–43)	42 (41–42)
Triglycerides	46 (45–46)	46 (45–46)	45 (44–45)
SBP	31 (30–31)	31 (30–31)	30 (30–30)
Simultaneous failure			
HbA_{1c} + LDL	61 (60–61)	62 (62–62)	63 (62–63)
HbA_{1c} + SBP	53 (53–54)	55 (55–55)	57 (57–57)
LDL + SBP	57 (56–57)	56 (56–57)	55 (55–56)
HbA_{1c} + triglycerides	61 (61–61)	62 (62–62)	63 (62–63)

*Control: HbA_{1c} <7.5% (58 mmol/mol); triglycerides <150 mg/dL; and SBP <130/140 mmHg and LDL <70/100 mg/dL for those with/without history of CVD at the time of second-line ADD initiation. LDL, triglycerides, and SBP proportions are calculated among users of lipid-modifying and antihypertensive drugs.

Among patients treated with a lipid-modifying drug, 43% had uncontrolled LDL over 2 years after baseline (Table 2), whereas 64/36% of those with/without a history of CVD failed to achieve LDL <70/100 mg/dL (data not shown). In this cohort, 46% had uncontrolled triglycerides over 2 years after baseline (Table 2), and the proportions were similar among those with/without history of CVD at baseline. Among patients, who were using an antihypertensive drug, 30% failed to control SBP during 2 years after intensification with a second-line ADD, whereas 49/24% of those with/without a history of CVD failed to achieve SBP <130/140 mmHg over 2 years.

Among patients with a baseline HbA_{1c} ≥7.5 and ≤9% (58–75 mmol/mol), 43, 46, and 48% failed to achieve HbA_{1c} <7.5% (58 mmol/mol) at 6, 12, and 24 months, respectively, irrespective of additional TI (Fig. 1). Among those who were using a lipid-modifying drug and had uncontrolled LDL at baseline (n = 45,802), the proportions of those who were uncontrolled at 6, 12, and 24 months were 71, 65, and 60%, and 81, 78, and 76% failed to control LDL at 6, 12, and 24 months among those who had a history of CVD at baseline (n = 15,105), respectively. In a similar way, more than 60% continued to have uncontrolled triglycerides among those who were uncontrolled at baseline. In patients using an antihypertensive drug and who had uncontrolled SBP at baseline, the proportions of those who were uncontrolled at 6, 12, and 24 months were 60, 55, and 51%, respectively, and more than 60% remained uncontrolled among those with history of CVD at baseline (n = 26,901).

Pairwise Risk Factor Control

Among patients who were using a lipid-modifying drug, apart from being on intensified ADD by design, ~62% failed to simultaneously control HbA_{1c} + LDL over 2 years after second-line ADD initiation (Table 2), whereas ~75/58% of those with/without a history of CVD failed to control both risk factors simultaneously (data not shown). Among those who were using an antihypertensive drug, 53, 55, and 57% failed to simultaneously control HbA_{1c} + SBP at 6, 12, and 24 months, respectively, after second-line ADD initiation. Among those with and without a history of CVD, 64–67% and 50–54%, respectively, failed to control both risk factors simultaneously (data not shown). Among those who were using drugs for lipid and blood pressure control (~70% of patients), more than one-half failed to control LDL + SBP over 2 years. Among patients who were using a lipid-modifying drug, ~62% failed to simultaneously control HbA_{1c} + triglycerides over 2 years after second-line ADD initiation.

Continued Risk Factor Burden Over 2 Years

Among those with at least 24 months of follow-up, 35% had continuously uncontrolled HbA_{1c} >7.5% (58 mmol/mol). The 2-year burden increased from 31% for those who intensified first-line ADD in 2005 to 41% for those who intensified therapy in 2014 (Fig. 2*A*). The 2-year burden increased from 28 to 36% and from 32 to 42% for those with/without history of CVD at baseline (Fig. 2*B* and *C*). In subcohort 2, the proportions initiating a second-line ADD with sulfonylurea (SU), thiazolidinedione (TZD), insulin (INS), glucagon-like peptide 1 receptor agonist (GLP-1RA), or dipeptidyl peptidase 4 inhibitor (DPP-4i) were 56, 12, 12, 4, and 16%, respectively. The

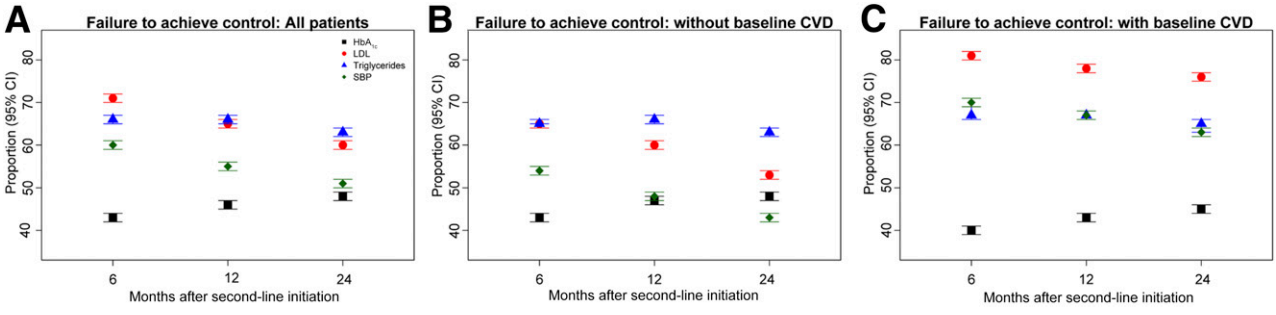

Figure 1—*A–C*: Among uncontrolled patients at baseline, the proportion (95% CI) of those who failed to control individual risk factors at 6, 12, and 24 months after second-line ADD initiation. Uncontrolled: HbA_{1c} ≥7.5 and ≤9% (58–75 mmol/mol); triglycerides ≥150 mg/dL; and SBP ≥130/140 mmHg and LDL ≥70/100 mg/dL for those with/without history of CVD at the time of second-line ADD initiation. Control: HbA_{1c} <7.5% (58 mmol/mol); triglycerides <150 mg/dL; and SBP <130/140 mmHg and LDL <70/100 mg/dL for those with/without history of CV disease at the time of second-line ADD initiation. LDL, triglycerides, and SBP proportions are calculated among users of lipid-modifying and blood pressure–lowering drugs.

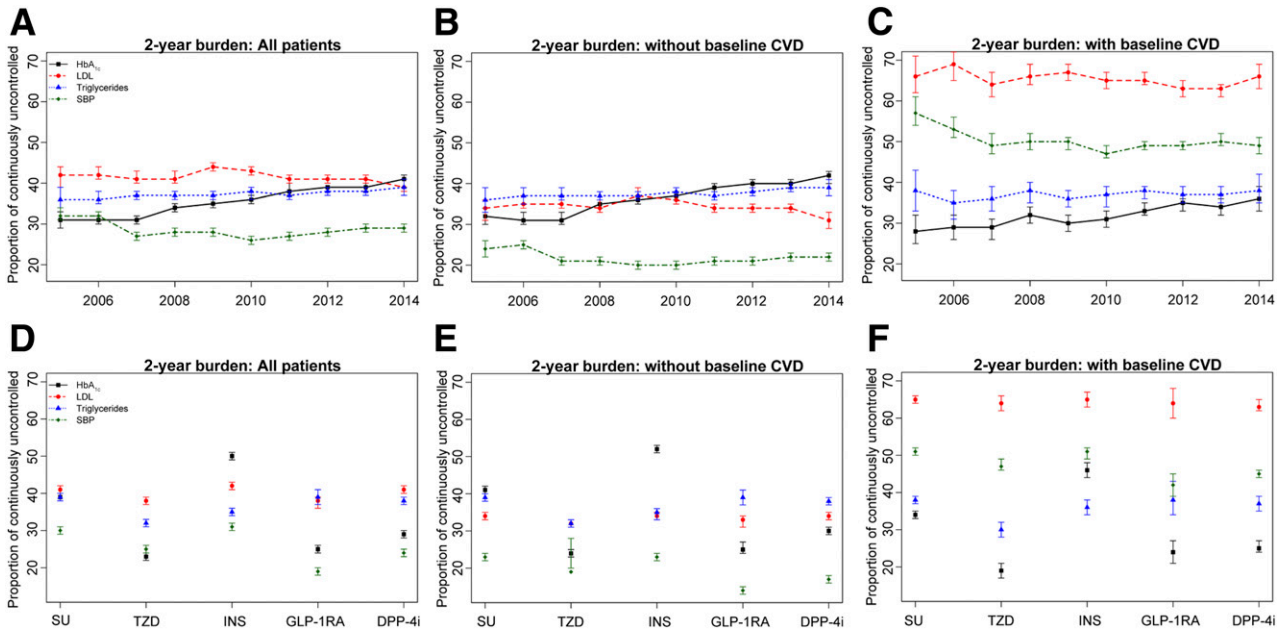

Figure 2—Proportion of continuously uncontrolled patients over 2 years after second-line ADD initiation, by the year of drug initiation (*A–C*) and by second-line ADD (*D–F*). Uncontrolled: $HbA_{1c} \geq 7.5\%$ (58 mmol/mol); triglycerides ≥150 mg/dL; and SBP ≥130/140 mmHg and LDL ≥70/100 mg/dL for those with/without history of CVD.

proportions of those with continuously uncontrolled HbA_{1c} were lower among those who initiated a second-line ADD with GLP-1RA (95% CI 24–26) and TZD (95% CI 23–24), followed by DPP-4i (95% CI 28–30), and significantly higher for SU (95% CI 39–40) and INS (95% CI 50–51) (Fig. 2*D–F*).

Among those who were using a lipid-modifying drug and had at least 2 years of follow-up, 41% had continuously uncontrolled LDL (Fig. 2*A*). In patients with/without a history of CVD at baseline, 65/33% had continuously uncontrolled LDL over 2 years of baseline (Fig. 2*B* and *C*). In this cohort, 37% had continuously uncontrolled triglycerides of >150 mg/dL (Fig. 2*A–C*).

Among those who were prescribed an antihypertensive drug and had at least 2 years of follow-up, 27–33% had continuously uncontrolled SBP (Fig. 2*A*). Among those with/without history of CVD at baseline, 51/21% had continuously uncontrolled SBP over 2 years of baseline (Fig. 2*B* and *C*).

CONCLUSIONS

The novelty of this EMR-based retrospective cohort study includes the holistic evaluation of the simultaneous glycemic and CV risk factor burden over 2 years in patients with type 2 diabetes who were treated with cardioprotective medications apart from receiving intensified therapy for glycemic control. We are not aware of any study that has simultaneously evaluated risk factor control in such a patient cohort with type 2 diabetes. An additional novelty of the study is the extensive assessment of the trend in risk factor control over a decade since 2005, especially covering the time frame of the availability of newer antidiabetic therapies. Although a number of studies have evaluated therapeutic inertia in glycemic and CV risk factor management in patients with type 2 diabetes (9–11,18,24), population-level assessments of the persistent risk factor burden after TI are scarce.

In this real-world study based on an ambulatory and primary care database from the U.S. in incident type 2 diabetes patients from 2005 receiving lipid-lowering and antihypertensive medications in addition to intensified antidiabetic therapy, we have observed that in this high-risk population, irrespective of baseline control, *1*) more than 40% of patients do not meet the 7.5% (58 mmol/mol) target after 2 years after metformin intensification, *2*) long-term glycemic burden has increased over the last decade, *3*) approximately one-third of patients have consistently uncontrolled lipids and SBP, and *4*) more than one-half fail to control two CV risk factors simultaneously.

The results of this study clearly demonstrate persistent glycemic and CV risk factor burden among patients who are using multiple medications for glucose, lipid, and blood pressure control. Three of five patients who are already receiving intensified treatment are failing to simultaneously control glucose level and at least one CV risk factor. We recognize that a significant proportion of the study cohort is at high risk, with 22% having a history of CVD at baseline, whereas 13% experienced at least one CV event within 6 months of follow-up. We have observed that ~70–76% of patients are failing to simultaneously control glucose level and two CV risk factors and that ~80% are failing to control HbA_{1c}, LDL, triglycerides, and SBP simultaneously. Also, the proportions of those who fail to control CV risk factors are not reducing over time, and glycemic burden has increased during the last decade.

The latest analysis of NHANES data from 2007 to 2014 for 2,677 patients with type 2 diabetes suggested a decline in the achievement for the individualized HbA_{1c} target from 70 to 64% (8). In our study cohort of ~277,000 patients with incident type 2 diabetes from 2005, we also observed an increasing trend in the proportion of patients failing to control the HbA_{1c} level (31–41% from 2005 to 2016) over 2 years after TI from 2005 to 2014.

In our study cohort, 84 and 63% of patients with and without a history of CVD were on lipid-modifying therapy, which is higher than the observed 52% reported in NHANES 2003–2012 (25). Although statin prescribing patterns are increasing, using U.S. Medical Expenditure Panel Survey (MEPS) data, Salami et al. (26) reported that use of high-intensity statins was only 18–20% in patients with diabetes and no atherosclerotic CVD. Similarly, Abdallah et al. (27) reported that among 1,300 patients with diabetes, 88% were prescribed statins at the time of hospital discharge for acute myocardial infarction, whereas only 22% were prescribed intensive statin therapy. Population aging, therapy nonadherence, and inadequate TI when needed (therapeutic inertia) may explain the patterns observed in our study. Further studies investigating intensification patterns for lipid and blood pressure control and long-term consequences of not intensifying therapy when needed are required in patients with diabetes.

Approximately 80% of patients in the study cohort were prescribed at least one antihypertensive therapy, with ~30% having uncontrolled SBP at baseline (by our control definition). During 2 years of follow-up, 49% of patients with a history of CVD consistently had SBP above the limit. Recently published data from NHANES 2011–2016 suggests that 74–80% of U.S. adults with diabetes have hypertension (as defined by American College of Cardiology criteria), and ~50% of them fail to control SBP, similar to our findings (28). We have not observed any change in the trend of SBP burden since 2008 for patients with and without CVD. Using data from NHANES 1999–2000, Saydah et al. (29) reported that only 7% (95% CI 2.8–11.9) of adults with diabetes attained an HbA_{1c} <7%, blood pressure <130/80 mmHg, and total cholesterol <200 mg/dL. In our study, we observed that over 2 years after second-line ADD initiation, ~80% failed to control (according to our definition) HbA_{1c}, SBP, LDL, and triglycerides simultaneously.

In general, the CEMR database is representative of the U.S. population in age and ethnic subgroups; however, higher proportions of white Caucasians and patients from northeastern and midwestern states are represented in the CEMR (30). The distribution of CV risk factors was similar to the prospective national health surveys (15). A large cohort size, with an average of 3.7 years of follow-up after metformin intensification, ensures reliable estimates have been reported in the current study. Drug use data available from patients' medication lists, along with prescribing information and the robust data mining methodologies applied, bring additional value to this study (17,31). However, there is always a discrepancy between prescription information and the actual intake of medication in real-world studies. The choice of the study cohort based on a new diagnosis of diabetes (from 2005) after registration into the EMR was primarily based on data quality considerations, apart from our intention to ensure that the cohort had equal opportunity to access newer antidiabetic therapy, including incretins. Although ~20% of patients in the U.S. are prescribed a nonmetformin ADD as the first-line therapy (18), we chose to consider postmetformin TI only. These aspects may have introduced some selection bias. Additional limitations include nonavailability of data on socioeconomic characteristics, diet, physical activity, and medication adherence.

To conclude, with approximately one-quarter of the study cohort being at a very high risk, we have observed alarming trends of population-level glycemic and CV risk factor control, whereas the risk factor burden has not reduced during the last decade. Although treatment guidelines and population education are constantly improving, the cardiovascular disease burden and associated costs of diabetes management are unlikely to reduce in the near future.

Acknowledgments. O.M. thanks her cosupervisors Dr. Ross Young and Dr. Louise Hafner of Queensland University of Technology, Brisbane, Australia.

Funding. Melbourne EpiCentre acknowledges support from the National Health and Medical Research Council and the Australian Government's National Collaborative Research Infrastructure Strategy initiative through Therapeutic Innovation Australia. O.M. acknowledges receipt of a PhD scholarship from Queensland University of Technology. No separate funding was obtained for this study.

Duality of Interest. S.K.P. has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical, and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator-initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi, and Pfizer. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. O.M. conducted the data extraction. O.M. and S.K.P. were responsible for the primary design of the study, jointly conducted the statistical analyses, and developed the first draft of the manuscript. X.C. contributed to the finalization of the manuscript and to the study design. 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. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544–1550

2. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes [published correction appears in Diabetologia 2009; 52:2470]. Diabetologia 2009;52:2288–2298

3. Arnold SV, Kosiborod M, Wang J, Fenici P, Gannedahl G, LoCasale RJ. Burden of cardiorenal-metabolic conditions in adults with type 2 diabetes within the Diabetes Collaborative Registry. Diabetes Obes Metab 2018;20:2000–2003

4. American Diabetes Association. Summary of revisions: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S4–S6

5. Khunti K, Kosiborod M, Ray KK. Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: time to overcome multifactorial therapeutic inertia? Diabetes Obes Metab 2018;20:1337–1341

6. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013; 368:1613–1624

7. 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

8. Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. Achievement of glycated hemoglobin goals in the US remains unchanged through 2014. Diabetes Ther 2017;8:863–873

9. Montvida O, Shaw JE, Blonde L, Paul SK. Long-term sustainability of glycaemic achievements with second-line antidiabetic therapies in patients with type 2 diabetes: a real-world study. Diabetes Obes Metab 2018;20:1722–1731

10. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. Diabetes Obes Metab 2018;20:427–437

11. 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

12. 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
13. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States*. Atlanta, GA, US Department of Health and Human Services, 2018
14. 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
15. 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
16. 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
17. 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
18. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: real-world evidence in patients newly diagnosed with type 2 diabetes. Diabetes Care 2018;41:69–78
19. 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
20. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284
21. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23(Suppl. 2):1–87
22. Stone NJ, Robinson JG, Lichtenstein AH, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–2934
23. Thomas G, Klein K, Paul S. Statistical challenges in analysing large longitudinal patient-level data: the danger of misleading clinical inferences with imputed data. J Indian Soc Agric Stat 2014;68:39–54
24. Desai U, Kirson NY, Kim J, et al. Time to treatment intensification after monotherapy failure and its association with subsequent glycemic control among 93,515 patients with type 2 diabetes. Diabetes Care 2018;41:2096–2104
25. Mercado CI, Gregg E, Gillespie C, Loustalot F. Trends in lipid profiles and descriptive characteristics of U.S. adults with and without diabetes and cholesterol-lowering medication use-National Health and Nutrition Examination Survey, 2003-2012, United States. PLoS One 2018;13:e0193756
26. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. JAMA Cardiol 2017;2:56–65
27. Abdallah MS, Kosiborod M, Tang F, et al. Patterns and predictors of intensive statin therapy among patients with diabetes mellitus after acute myocardial infarction. Am J Cardiol 2014;113:1267–1272
28. Muntner P, Whelton PK, Woodward M, Carey RM. A comparison of the 2017 American College of Cardiology/American Heart Association blood pressure guideline and the 2017 American Diabetes Association diabetes and hypertension position statement for U.S. adults with diabetes. Diabetes Care 2018;41:2322–2329
29. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291:335–342
30. Brixner DI, McAdam-Marx C, Ye X, et al. Six-month outcomes on A1C and cardiovascular risk factors in patients with type 2 diabetes treated with exenatide in an ambulatory care setting. Diabetes Obes Metab 2009;11:1122–1130
31. Owusu Adjah ES, Montvida O, Agbeve J, Paul SK. Data mining approach to identify disease cohorts from primary care electronic medical records: a case of diabetes mellitus. Open Bioinform J 2017;10:16–27