WHITEPAPER

Type 2 Diabetes and Management of Cardiovascular and Renal Comorbidities: A Cohort Analysis with Case Study Using Electronic Health Records

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ABBREVIATIONS

ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
BP	Blood Pressure
CCM	Chronic Care Model
CDC	Centers for Disease Control
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcomes Trial
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl Peptidase 4
EASD	European Association for the Study of Diabetes
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
FDA	Food and Drug Administration
GLP-1	Glucagon-Like Peptide 1
HbA1c	Hemoglobin A1c
HCP	Healthcare Provider
HF	Heart Failure
ICD-9	International Classification of Disease-Ninth Revision
ICD-10	International Classification of Disease-Tenth Revision
LOINC	Logical Observation Identifier Names and Codes
MACE	Major Adverse Cardiovascular Events
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NLP	Natural Language Processing
QoL	Quality of Life
RAAS	Renin-Angiotensin-Aldosterone System
RCT	Randomized Clinical Trial
RWD	Real-World Data
RWE	Real-World Evidence
SBP	Systolic Blood Pressure
SGLT2	Sodium-Glucose Cotransporter 2
SU	Sulfonylurea
T2D	Type 2 Diabetes
TZ	Thiazolidinedione
UACR	Urine Albumin-to-Creatinine Ratio

EXECUTIVE SUMMARY

Diabetes is a chronic metabolic disorder affecting over 30 million Americans, most of whom (up to 95%) have a diagnosis of type 2 diabetes. Diabetes confers substantial independent risk of atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease; in turn, these comorbidities, which share common pathophysiologic risk with diabetes and are likely to be included in comprehensive diabetes management plans, amplify mortality risk in individuals living with diabetes. The complexity of interactions between type 2 diabetes, concordant comorbidities, and ensuing complications requires a clinical approach that manages risk while maintaining guideline-specified therapeutic targets. With the addition of new drug classes and an emphasis on self-management along with shared decision-making, more patients are achieving individualized treatment goals. However, many patients struggle to meet targets for glycemic control or reduced cardiovascular risk. Inconsistencies in patient care quality suggest healthcare system-level improvements may enable care teams, empower patients, and reduce therapeutic inertia (failure to intensify therapy when treatment targets are not met).

This paper summarizes the challenges associated with concordant comorbidities in individuals living with type 2 diabetes and further explores how real-world evidence and natural language processing may be used to offer insight regarding opportunities for management. Using de-identified data from an electronic health record platform Practice Fusion, a Veradigm™ offering, a cohort analysis with case study was undertaken to 1) characterize ambulatory patients according to key demographics and comorbidities, 2) explore adoption of three of the latest glucose-lowering drug classes, and 3) evaluate the impact of concordant comorbidities on responsiveness to treatment intensification. The study identified one patient cohort as having greater incidence of microvascular and macrovascular complications, with more visits to healthcare providers. Forty-one percent (41%) of HbA1c values were supplemented through NLP enhancement. Across the cohorts, treatment intensification was associated with more patients achieving HbA1c values of less than 7%. Opportunities may exist for consideration of glucose-lowering drug classes with strong evidence of cardiovascular risk reduction and possibly nephro-protective effects to address unmet needs. Future studies that leverage real-world data from electronic health platforms may provide insight into drug research and development along with increased support for individualized diabetes management plans.

INTRODUCTION

Diabetes is a chronic metabolic disorder affecting over 30 million Americans, most of whom (up to 95%) have a diagnosis of type 2 diabetes mellitus (T2D). T2D is characterized by resistance to insulin, inadequate insulin secretion, and excessive or inappropriate glucagon secretion leading to chronic hyperglycemia (Khadori, 2019). Individuals aged 45 or older with a family history of diabetes, who are overweight and physically inactive, are more likely to develop T2D (NIDDK, 2016).

Economic costs attributable to diabetes are substantial.

- In 2017, the total estimated cost of diabetes in the US was $327 billion, with direct medical costs and reduced productivity accounting for $237 billion and $90 billion, respectively (American Diabetes Association [ADA], 2018).
- The rising economic burden of diabetes from 2012 to 2017 was due to increases in prevalence (11%) and in the cost per person (13%) (ADA, 2018).
- An estimated 1 in 4 US healthcare dollars are spent on care costs for individuals with diabetes (ADA, 2018).
- Out-of-pocket costs are higher for diabetes than for most other chronic conditions; preventive services may be underused owing to cost pressure (Piette and Kerr, 2006).

Diabetes is associated with significant morbidity and mortality.

- Among primary diagnosis groups, diabetes was ranked fifth for office visits (34.6 million in 2015) in a recent ambulatory medical care survey (US Department of Health and Human Services, 2015).
- Adults with a diagnosis of diabetes made nearly 14 million visits in a single year (2014) to emergency departments, according to a national hospital ambulatory survey (US Department of Health and Human Services, 2014).
- Diabetes was the seventh leading cause of death in the US in 2015 (Centers for Disease Control, 2017).

Comorbidities and complications in diabetes are common and challenging.

- Most adults with diabetes have one or more co-existing chronic comorbidities that increase rates of adverse events, risk of hospitalization, and mortality; over 40% of patients with T2D were reported to have 3-4 comorbidities in a cross-sectional analysis of electronic health record (EHR) data (2008-2012) (Lin et al, 2015).
- Atherosclerotic cardiovascular disease (ASCVD), hyperlipidemia or hypercholesterolemia, hypertension, heart failure (HF), obesity, and chronic kidney disease (CKD) are commonly occurring comorbidities in patients with T2D (Lin et al, 2015; Pantalone et al, 2015). Such vascular, metabolic, and renal comorbidities are considered to be "concordant" as they share common pathophysiologic risk with diabetes; further, they are likely to be included in comprehensive management plans in support of diabetes care (Piette and Kerr, 2006; Magnan et al, 2015a; Magnan et al, 2015b).
- Diabetes confers substantial independent risk of ASCVD and HF; in turn, ASCVD and HF confer greater risk of morbidity and mortality in patients with T2D (Davies et al 2018; Rosano et al, 2017). Patients with T2D and comorbid CKD have substantially increased all-cause and cardiovascular mortality risk relative to patients without comorbid CKD (Afkarian et al, 2013).
- In a cohort registry, having a glycated hemoglobin (HbA1c) level outside of target range was shown to be a strong predictor of adverse cardiovascular outcomes; HbA1c level, high body mass index (BMI), and renal dysfunction were among the strongest predictors of hospitalization for HF (Rawshani et al, 2018).

- In a survey of over 900 primary care patients with T2D, HF, depression, and microvascular complications (i.e., nephropathy, neuropathy, and retinopathy) were shown to have the greatest negative impact on quality of life (QoL) (Wexler et al, 2006).
- A trial designed to satisfy regulatory requirements for cardiovascular safety reported macrovascular complications (myocardial infarction, stroke) were associated with significant decreases in health-related quality of life (QoL), most notably in the initial post-event period, for patients with T2D (Briggs et al, 2017).
- In addition to affecting resource utilization, overall disease management, and treatment outcomes, the presence of multiple comorbidities may seriously limit the ability of patients to self-manage their diabetes (Piette and Kerr, 2006).

MANAGEMENT OF T2D, COMORBIDITIES, AND COMPLICATIONS

Multiple reinforcing neurohormonal, hemodynamic, immunologic, and metabolic mechanisms link T2D with concordant comorbidities. Of particular concern is the interplay between T2D and cardiorenal dysfunction, which may involve advancing atherosclerosis, activation of the renin-angiotensin-aldosterone system (RAAS), hypertension, increased oxidative stress, systemic inflammation, and microvascular endothelial dysfunction (Zelniker and Braunwald, 2018; Rosano et al, 2017). The complexity of interactions between T2D, concordant comorbidities, and their ensuing complications requires an approach that manages risk while maintaining individualized therapeutic targets (ADA, 2019a). To this end, initial and follow-up provider visits should assess the risk or presence and treatment of ASCVD and HF; the risk or presence, staging, and treatment of CKD; and risks associated with glucose-lowering treatment, particularly hypoglycemia (ADA, 2019b).

Specific goals of T2D management include prevention or delay of complications and maintenance or improvement in QoL, both accomplished through glycemic control and risk factor management. While more patients with diabetes are achieving treatment targets, survey data indicate a substantial proportion of patients do not meet targets for glycemic control or reduced cardiovascular risk (Ali et al, 2013; Carls et al, 2017). Another survey study reported patients with complex comorbidities have distinct challenges (e.g., lower diabetes prioritization and ability to self-manage) affecting goal-based care (Kerr et al, 2007).

Across provider settings, inconsistencies in diabetes care quality suggest system-level improvements may be warranted (ADA 2019c). A coordinated chronic care model (CCM) with six core elements—delivery system design (moving from reactive to proactive care), clinical information systems (using registries that provide patient-specific and population-based support to the care team), decision support (basing care on evidence-based guidelines), community resources (to support healthy lifestyles), health systems (to create a quality-oriented culture) and self-management support—prepares and enables care teams, empowers patients, and reduces risk of therapeutic inertia (failure to intensify treatment when targets are not met) (Davies et al, 2018; ADA, 2019c).

PHARMACOTHERAPEUTIC APPROACHES TO GLYCEMIC TREATMENT AND RISK FACTOR REDUCTION IN T2D

Pharmacologic approaches to glycemic therapy recommended by the ADA in the 2019 Standards of Medical Care in Diabetes align with those provided in a consensus report written collaboratively with the European Association for the Study of Diabetes (EASD) (ADA, 2019d; Davies et al, 2018). ADA/EASD 2019 recommendations for treatment of cardiovascular disease and risk management, including recommendations outlining the use and benefits of agents from two glucose-lowering drug classes with cardiovascular benefit (and possibly nephro-protective effects), are endorsed by the American College of Cardiology (ACC, 2018).

Treatment of hyperglycemia in T2D is based in large part on improvements in diet and exercise; glucose-lowering medications with proven efficacy, tolerability, and safety; hypoglycemic risk; concordant and discordant comorbidities; impact on weight; cost of care; and patient preferences (ADA, 2019d). Treatment decisions should be adjusted according to social context (e.g., food insecurity, housing stability, financial barriers) (ADA, 2019a and 2019c).

Glucose-lowering therapy commences with diagnosis. Along with comprehensive lifestyle management, metformin is preferred as first-line therapy owing to its effectiveness and safety and potential to reduce the risk of cardiovascular events (evidence level, A) (ADA, 2019e). If HbA1c levels remain above target, second-line agents from six drug classes may be added. In patients without established ASCVD, HF, and/or CKD who have a need to minimize hypoglycemia, pharmacotherapies recommended for a first-round of treatment intensification include dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and thiazolidinediones (ADA, 2019e). If above-target HbA1c levels continue, the addition of a second intensifying agent is recommended; if elevated glycation persists, a sulfonylurea or basal insulin is added (ADA, 2019e).

For patients with ASCVD who are on metformin therapy or using diet and exercise to improve glycemic control, glucose-lowering agents with strong evidence of cardiovascular risk reduction (especially those with proven reduction of cardiovascular death and therefore benefit) in cardiovascular outcomes trials (CVOTs) designed to evaluate cardiovascular safety are recommended at the start of treatment intensification (ADA, 2019f). Specifically, in patients with established ASCVD, HF, and/or CKD, either SGLT2 inhibitors or GLP-1 receptor agonists are recommended for initial intensification based on findings from CVOTs, with DPP4 inhibitors or other drug classes recommended for further intensification (**Table 1**).

TABLE 1 | Glucose-Lowering Medication Classes for Treatment Intensification in T2D with Established ASCVD, HF, and/or CKD[1]

Class	ASCVD Predominates	HF or CKD Predominates
SGLT2 inhibitors	With proven CVD benefit[2], if eGFR is adequate	With evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
GLP-1 receptor agonists	With proven CVD benefit[2]	With proven CVD benefit,[2] if SGLT2 not tolerated or contraindicated or if eGFR less than adequate
For further intensification or if SGLT-2 inhibitor and/or GLP-1 receptor agonist not tolerated		
DPP-4 inhibitors	If not on GLP-1 receptor agonists	In the setting of HF, not saxagliptin, if not on GLP-1 receptor agonist
Basal insulin	Degludec or U100 glargine have demonstrated CVD safety	Degludec or U100 glargine have demonstrated CVD safety
Thiazolidinediones	Low dose for TZ may be better tolerated though less well studied for CVD effects	Avoid in the setting of HF
Sulfonylureas	Choose later generation SU with lower risk of hypoglycemia	Choose later generation SU with lower risk of hypoglycemia

[1] First-line therapy includes metformin and comprehensive lifestyle management (body weight and physical activity); if HbA1c is above target, proceed to additional medication classes listed.

[2] "With proven CVD benefit" means there is label indication of reducing CVD events.

Abbreviations: ASCVD=atherosclerotic cardiovascular disease; HF=heart failure; CKD=chronic kidney disease; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; CVOTs=cardiovascular outcomes trials; TZ=thiazolidinediones; SU=sulfonylureas; SGLT2=sodium-glucose cotransporter 2; GLP-1=glucagon-like peptide 1; DPP-4=dipeptidyl peptidase 4.

Adapted from ADA, 2019e.

SGLT2 Inhibitors

Orally administered SGLT2 inhibitors inhibit glucose reabsorption in the renal proximal tubule, reducing plasma glucose levels and promoting urinary glucose and sodium excretion (van der Wal et al, 2017). SGLT2 inhibitors reduce blood pressure, enhance lipolysis, and reduce fat mass and body weight (Vallon and Thomson, 2017). When these agents are not taken concurrently with basal insulin or agents promoting insulin secretion, the risk of hypoglycemia is low (Das et al, 2018).

In CVOTs, two SGLT2 inhibitors (canagliflozin, empagliflozin) significantly reduced the risk of three-point major adverse cardiovascular events (MACE) (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) compared with placebo (Zinman et al, 2015; Neal et al, 2017). Cardiovascular benefit was demonstrated for patients with but not without ASCVD. SGLT2 inhibitors (canagliflozin, empagliflozin, dapagliflozin) also reduced the risk of hospitalization for HF compared with placebo (Fitchett et al, 2016; Rådholm et al, 2018; Wiviott et al, 2019). A meta-analysis of CVOTs (canagliflozin, empagliflozin, dapagliflozin) demonstrated reductions in the risk of MACE (11%) and hospitalization for HF (23%) (Zelniker et al, 2019).

The same meta-analysis showed substantial reduction in the progression of renal disease (45%) (Zelniker et al, 2019). In RCTs, use of SGLT2 inhibitors (canagliflozin, empagliflozin) was associated with slower progression of albuminuria and lower rates of clinically relevant renal events versus placebo when added to standard care (Wanner et al, 2016; Neal et al, 2017). Results of a recent double-blind, randomized clinical trial (RCT) in which patients with T2D and albuminuric CKD received canagliflozin or placebo added to RAAS blockade and baseline diabetic therapy demonstrated superior outcomes for the SGLT2 inhibitor (i.e., 30% lower relative risk for the primary composite of end-stage kidney disease and up to 30% lower risk of unfavorable cardiovascular outcomes) (Perkovic et al, 2019).

Four SGLT2 inhibitors—canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin—are approved as adjuncts to diet and exercise to improve glycemic control in adults with T2D. Canagliflozin and empagliflozin are additionally indicated to reduce the risk of MACE or to reduce the risk of cardiovascular death, respectively, in adults with T2D and established cardiovascular disease. For patients with T2D and ASCVD, SGLT2 inhibitors with proven cardiovascular benefit are recommended as part of glucose-lowering regimens (evidence level, A) (ADA, 2019e). For patients with ASCVD who are at risk for HF or have co-existing HF, the use of SGLT2 inhibitors is preferred (ADA, 2019e; Davies et al, 2018). For patients with T2D and CKD, with or without ASCVD, SGLT2 inhibitors that reduce CKD progression are recommended (**Table 1**) (ADA, 2019e; Davies et al, 2018).

GLP-1 Receptor Agonists

Injectable GLP-1 receptor agonists are incretin mimetics that enhance glucose-dependent insulin secretion and delay postprandial glucagon production; these agents also decrease food intake and slow gastric emptying (van der Wal et al, 2017). In addition to promoting weight loss, GLP-1 receptor agonists have a low risk of hypoglycemia when not used with basal insulin or insulin secretagogues (Pratley et al, 2008).

The cardiovascular safety of GLP-1 receptor agonists has been evaluated in CVOTs, with some trials (liraglutide, semaglutide, albiglutide, dulaglutide) demonstrating reduction in the risk of MACE (Marso et al, 2016a; Marso et al, 2016b; Hernandez et al, 2018; Eli Lilly, 2018) and other trials (lixisenatide, exenatide) reporting neither cardiovascular benefit nor harm (Holman et al, 2017; Pfeffer et al, 2015). No significant effect on HF hospitalization was reported for GLP-1 receptor agonists (Marso et al, 2016a; Marso et al, 2016b; Holman et al, 2017; Marguilies et al, 2016; Jorsal et al, 2017).

For new or worsening nephropathy, GLP-1 receptor agonists (liraglutide, semaglutide; dulaglutide) were reported to provide benefit, slowing progression of albuminuria (Marso et al, 2016b; Mann et al, 2017; Tuttle et al, 2018). A post-hoc analysis of a CVOT demonstrated lixisenatide added to usual care reduced progression of urine albumin-to-creatinine ratio (UACR) by 39% compared with placebo in patients with T2D without severe renal impairment but with a recent coronary artery event (Muskiet et al, 2018).

GLP-1 receptor agonists are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2D. One agent (liraglutide) is additionally indicated to reduce the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease. GLP-1 receptor agonists with proven cardiovascular benefit are recommended for patients with T2D in

whom ASCVD or HF or CKD manifest as predominant comorbidities (evidence level, A) (ADA, 2019e). For patients with T2D and CKD, with or without ASCVD, the use of a GLP-1 receptor agonist shown to reduce CKD progression is recommended (**Table 1**) (ADA, 2019e; Davies et al, 2018).

DPP-4 Inhibitors

Orally administered DPP-4 inhibitors increase insulin synthesis and decrease glucagon release by inhibiting hydrolysis of incretins (GLP-1 and gastric inhibitory polypeptide) (van der Wal et al, 2017). DPP-4 inhibitor effects on body weight are neutral; these agents do not cause hypoglycemia in the absence of agents that may increase risk (Pratley et al, 2008).

In CVOTs conducted for DPP-4 inhibitors, one (saxagliptin) reported an increased risk of HF, others (sitagliptin, linagliptin) showed no difference in HF hospitalization compared with placebo, and another (alogliptin) showed a numerical but non-significant difference without an increase in mortality (Scirica et al, 2013; Green et al, 2015; Zannad et al, 2015; McGuire et al, 2018). Adding DPP-4 inhibitors to standard care did not increase risk of MACE (Scirica et al, 2013; White et al, 2013; Green et al, 2015).

From a renal perspective, no significant benefit for a DPP-4 inhibitor (linagliptin) was observed for a kidney composite outcome (time to first occurrence of sustained end-stage kidney disease, renal death, or sustained decrease of ≥40% in eGFR from baseline) compared with placebo, although there were reductions in the progression of albuminuria and a composite microvascular endpoint versus placebo (Rosenstock et al, 2019; Schnell et al, 2019).

DPP-4 inhibitors are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2D. DPP-4 inhibitors are recommended for treatment intensification if there is a need to minimize hypoglycemia in the absence of ASCVD or CKD, for further intensification or if GLP-1 receptor agonists and/or SGLT2 inhibitors are not tolerated in patients with ASCVD (but not with a GLP-1 receptor agonist), or in the setting of HF (but not saxagliptin) if not taking a GLP-1 receptor agonist (**Table 1**) (Davies et al., 2018).

Combination Studies with SGLT2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors

Combination therapy using drugs with different mechanisms of action may provide additive or complementary benefit for glycemic control and risk reduction. In RCTs that evaluated the addition of GLP-1 receptor agonists (exenatide, dulaglutide, semaglutide) to ongoing treatment with SGLT2 inhibitors, the combination was shown to be superior to the combination of placebo and SGLT2 inhibitor in reducing HbA1c levels and body weight, all with reasonable tolerability (Frias et al, 2018; Ludvik et al, 2018; Zinman et al, 2019). Another study reported the addition of a DPP-4 inhibitor (saxagliptin) to SGLT2 inhibitor (dapagliflozin) therapy in patients poorly controlled with metformin led to greater improvement in glycemic control and was well tolerated (Rosenstock et al, 2015).

REAL-WORLD EVIDENCE IN T2D

Real-world evidence (RWE) has been defined by the US Food and Drug Administration (FDA) as clinical evidence of the use and of the benefits or risks of medical products (Corrigan-Curay et al, 2018; FDA 2018 and 2019). RWE is derived from real-world data (RWD)—data that is related to patient health status or to the delivery of healthcare. RWD is routinely collected from medical and prescription claims, patient and provider surveys, disease- and product-specific registries, and EHRs (Sherman et al, 2016; FDA, 2019).

In support of traditional T2D trials are the findings of RWE observational studies. For patients newly initiated on glucose-lowering therapies, the use of SGLT2 inhibitors was associated with lower rates of all-cause mortality and HF hospitalization (Kosiborod et al, 2017; Kosiborod et al, 2018). Interim results from another real-world study reported treatment with an SGLT2 inhibitor in routine clinical practice was associated with reduced risk of HF hospitalization (Boehringer Ingelheim, 2018). Another study demonstrated real-world effectiveness of an SGLT2 inhibitor in lowering HbA1c, body weight, and systolic blood pressure, regardless of age or baseline HbA1c levels (Johnson et al, 2017). In older (>65 yr) T2D patients, combination therapy with GLP-1 receptor agonists and SGLT2 inhibitors led to clinically meaningful reductions in HbA1c levels, body weight and systolic blood pressure, with minimal hypoglycemia and reasonable tolerability (Carretero et al, 2019).

As sources of RWE, registries and other observational studies provide opportunities for enabling clinical support and shared decision-making in acute-care and ambulatory patient settings. For example, registry report summary sheets contain general information (i.e., laboratory findings and medication lists) and may include embedded evidence-based guidelines and adherence metrics; these may be used to support treatment intensification in T2D, as directed by the physician (NIDDK, 2019). In keeping with a focus on shared decision-making and patient-centered care, clinical support recommendations made to both patients and their healthcare providers (HCPs) may be more effective than recommendations made to HCPs only (O'Connor et al, 2016).

COHORT ANALYSIS AND CASE STUDY

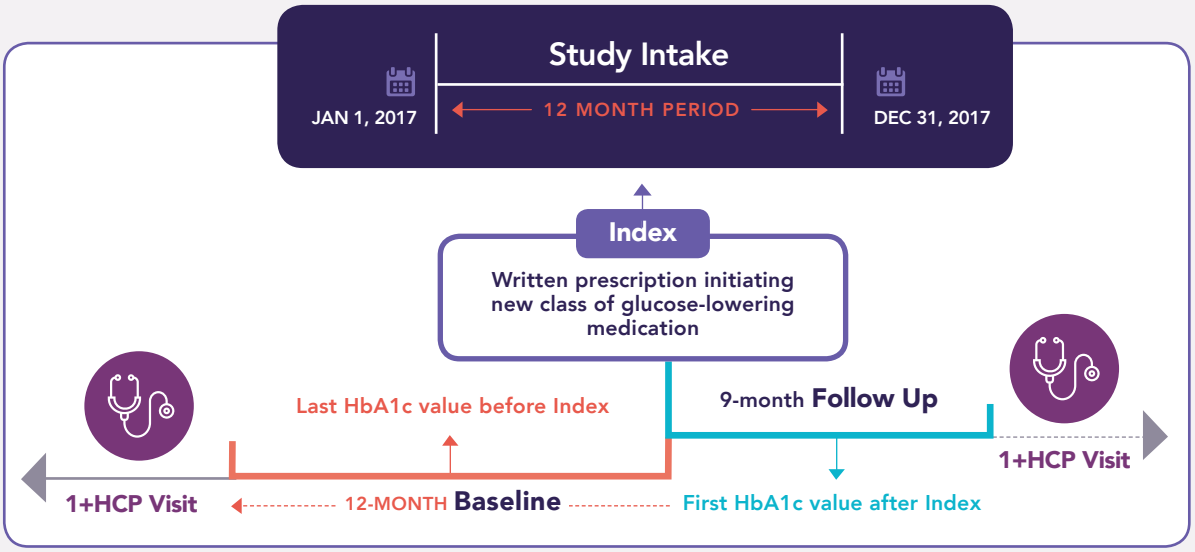
To explore how real-world observations may provide insight into the challenges of and opportunities for managing T2D, RWE was generated from de-identified RWD sourced from EHR Practice Fusion, a Veradigm™ offering. As the largest cloud-based EHR platform for ambulatory patients in the US, Practice Fusion enables secure, bi-directional communication between Practice Fusion and HCPs that provides a basis for exploring and supporting disease management during routine clinical care (Veradigm, 2019).

The objectives of this study were to 1) characterize adult ambulatory patients with T2D, 2) explore adoption of the three newest glucose-lowering drug classes, and 3) evaluate the impact of concordant comorbidities on responsiveness to treatment intensification.

Study Design

This retrospective, observational cohort analysis and case study evaluated de-identified data (demographics, vital signs, laboratory assessments, comorbidities, complications, prescription medications, and provider specialty) from adult ambulatory patients who received a prescription for a new glucose-lowering pharmacotherapy and who had glycated hemoglobin values before and after treatment intensification.

FIGURE 1 | **Study Design**



The study design is shown in **Figure 1**. Patients had to

- Have a documented diagnosis of T2D (by ICD-9-CM code or ICD-10-CM code transposed to ICD-9-CM)
- Have a prescription order initiating treatment from one of the following glucose-lowering classes: SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, insulin or insulin analogs, sulfonylureas, and thiazolidinediones, whether alone or in combination with metformin or with insulin during study intake between January 1st and December 31st, 2017 (the Index date); for the new prescription, patients could not have received a prescription previously from within the same medication class
- Be 18 years of age or older at Index
- Have continuity of care evident in the EHR platform (i.e., at least one HCP visit more than 12 months prior to Index and at least one HCP visit more than 9 months after Index)
- Have at least 1 HbA1c value recorded during the 12-month period prior to Index (Baseline)
- Have at least 1 HbA1c value recorded during the 9-month period following Index (Follow-up).

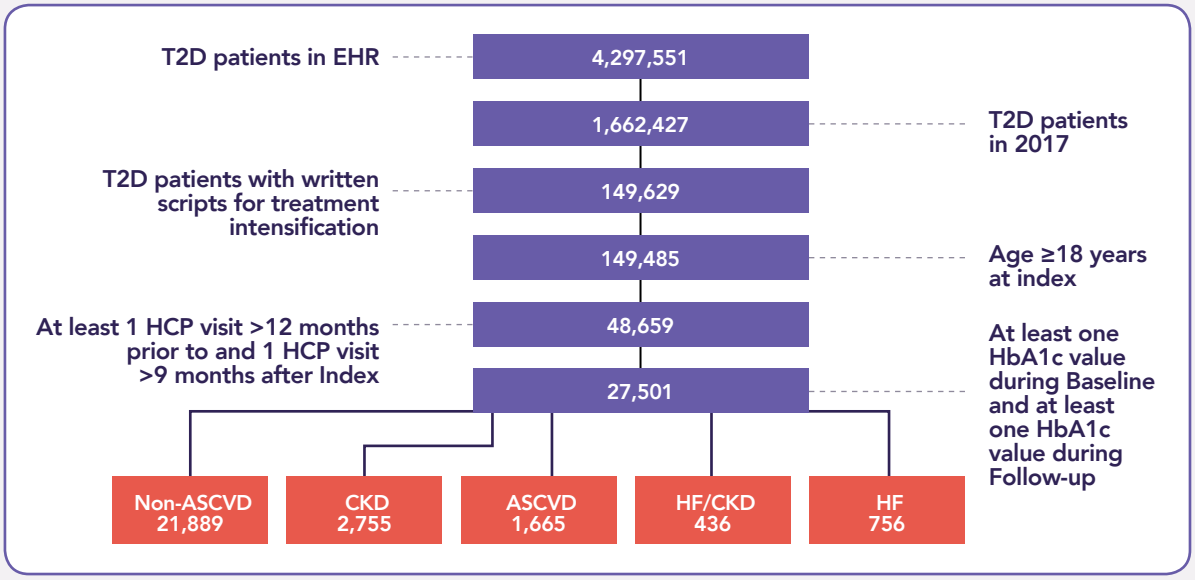
Patients were evaluated as a single group (all) and were also stratified according to concordant comorbidities, yielding the following five cohorts:

- Non-ASCVD (T2D without ASCVD, without HF, and without CKD)
- ASCVD (T2D with ASCVD, without HF, and without CKD)
- HF (T2D with HF, without CKD)
- CKD (T2D with CKD, without HF)
- HF/CKD (T2D with HF and CKD).

RESULTS

A total of 149,629 patients with T2D were provided a written prescription for treatment intensification during study intake (**Figure 2**) from glucose-lowering drug classes (**Table 1**). From this pool, 27,501 patients met additional criteria for age, continuity of care, and HbA1c assessments. Most patients (79.6%) were included in the non-ASCVD (also without HF or CKD) cohort; the other cohorts represented 10.0% (CKD), 6.1% (ASCVD), 2.7% (HF), and 1.6% (HF/CKD) of all patients.

FIGURE 2 | Sample Selection



Patient Characteristics

Table 2 shows the baseline demographics, baseline vital signs, and anti-hypertensive medications for the five cohorts. There were fewer females than males in the ASCVD (42.1%), CKD (46.6%), and HF/CKD (45.9%) cohorts. The mean age (SD) for the all-patient cohort (62.4 [12.0]) aligned with those reported in CVOTs (Scirica et al, 2013; White et al, 2013; Green et al, 2015; Pfeffer

TABLE 2 | Patient Demographics, Vital Signs, and Anti-hypertensive Medications

CHARACTERISTICS	Patients with T2D					
	All	non-ASCVD	ASCVD	HF	CKD	HF/CKD
PATIENTS, N (% OF ALL)						
Patients	27,501 (100.0)	21,889 (79.6)	1,665 (6.1)	756 (2.7)	2,755 (10.0)	436 (1.6)
GENDER, N (% OF COHORT)						
Female	13,503 (49.1)	10,953 (50.0)	701 (42.1)	364 (48.1)	1,285 (46.6)	200 (45.9)
Male	13,988 (50.9)	10,927 (49.9)	964 (57.9)	392 (51.9)	1,469 (53.3)	236 (54.1)
Not recorded	10 (0.0)	9 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
AGE, N (% OF COHORT) Unless Otherwise Indicated						
Age, mean yr (SD)	62.4 (12.0)	60.6 (11.8)	67.5 (10.1)	68.8 (11.5)	69.8 (10.3)	72.1 (9.6)
18-44 yr	2,077 (7.6)	1,983 (9.1)	29 (1.7)	18 (2.4)	43 (1.6)	4 (0.9)
45-64 yr	13,215 (48.1)	11,572 (52.9)	594 (35.7)	239 (31.6)	731 (26.5)	79 (18.1)
>65 yr	12,209 (44.4)	8,334 (38.1)	1,042 (62.6)	499 (66.0)	1,981 (71.9)	353 (81.0)
RACE, N (% OF COHORT)						
Caucasian	11,798 (42.9)	9,345 (42.7)	839 (50.4)	338 (44.7)	1,086 (39.4)	190 (43.6)
African American	3,530 (12.8)	2,672 (12.2)	199 (12.0)	141 (18.7)	430 (15.6)	88 (20.2)
Other	3,108 (11.3)	2,418 (11.0)	171 (10.3)	75 (9.9)	402 (14.6)	42 (9.6)
Not recorded	9,065 (33)	7,454 (34.1)	456 (27.4)	202 (26.7)	837 (30.4)	116 (26.6)
ETHNICITY, N (% OF COHORT)						
Hispanic/ Latino	4,281 (15.6)	3,352 (15.3)	286 (17.2)	83 (11.0)	482 (17.5)	78 (17.9)
Not Hispanic/ Latino	23,220 (84.4)	18,537 (84.7)	1,379 (82.8)	673 (89.0)	2,273 (82.5)	358 (82.1)
GEOGRAPHY, N (% OF COHORT)						
Northeast	5,854 (21.3)	4,811 (22.0)	435 (26.1)	139 (18.4)	405 (14.7)	64 (14.7)
Midwest	3,134 (11.4)	2,610 (11.9)	181 (10.9)	91 (12.0)	215 (7.8)	37 (8.5)
South	12,524 (45.5)	9,889 (45.2)	752 (45.2)	365 (48.3)	1,300 (47.2)	218 (50.0)
West	5,773 (21.0)	4,450 (20.3)	262 (15.7)	151 (20.0)	807 (29.3)	103 (23.6)
Not recorded	216 (0.8)	129 (0.6)	35 (2.1)	10 (1.3)	28 (1.0)	14 (3.2)

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TABLE 2 | Patient Demographics, Vital Signs, and Anti-hypertensive Medications *Continued*

CHARACTERISTICS	Patients with T2D					
	All	non-ASCVD	ASCVD	HF	CKD	HF/CKD
HISTORY OF SMOKING, N (% OF COHORT)						
Smoking	10,425 (37.9)	7,875 (36.0)	849 (51.0)	397 (52.5)	1,098 (39.9)	206 (47.2)
VITAL SIGNS, N (% OF COHORT) Unless Otherwise Indicated						
Weight	26,057 (94.7)	20,655 (94.4)	1,591 (95.6)	715 (94.6)	2,677 (97.2)	419 (96.1)
Weight, mean (SD)	202.5 (51.7)	203.7 (52.0)	196.8 (49.1)	210.3 (55.1)	195 (48.5)	202.1 (53.4)
BMI	26,057 (94.7)	20,655 (94.4)	1,591 (95.6)	715 (94.6)	2,677 (97.2)	419 (96.1)
BMI, mean (SD)	33.1 (7.3)	33.2 (7.3)	32.1 (6.8)	34.6 (8.1)	32.2 (7.1)	33.2 (7.5)
Blood pressure	26,854 (97.6)	21,314 (97.4)	1,634 (98.1)	749 (99.1)	2,723 (98.8)	434 (99.5)
Systolic, mean (SD)	131.3 (16.4)	131.1 (16.1)	131.9 (16.4)	130.9 (17.3)	132.7 (17.7)	130.9 (18.1)
Diastolic, mean (SD)	77.2 (10.1)	77.7 (10.0)	75.6 (9.9)	75.4 (10.7)	74.7 (10.1)	72.9 (11.2)
SBP/DBP ≥140/≥90 mmHg	2,222 (8.1)	1,874 (8.6)	106 (6.4)	64 (8.5)	152 (5.5)	26 (6.0)
ANTI-HYPERTENSIVE DRUGS, N (% OF COHORT)						
Aldosterone receptor antagonists	994 (3.6)	565 (2.6)	57 (3.4)	154 (20.4)	127 (4.6)	91 (20.9)
ACE inhibitors	13,884 (50.5)	10,847 (49.6)	925 (55.6)	409 (54.1)	1,460 (53.0)	243 (55.7)
Angiotensin receptor blockers	9,919 (36.1)	7,435 (34.0)	672 (40.4)	344 (45.5)	1,268 (46.0)	200 (45.9)
Calcium channel blockers	3,716 (13.5)	2,617 (12.0)	281 (16.9)	163 (21.6)	544 (19.%)	111 (25.5)
Thiazide diuretics	9,784 (35.6)	7,489 (34.2)	610 (36.6)	295 (39.0)	1,221 (44.3)	169 (38.8)

Abbreviations: T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; HF=heart failure; CKD=chronic kidney disease; SD=standard deviation; BMI=body mass index; BP=blood pressure; SBP/DBP=systolic blood pressure/diastolic blood pressure; ACE=angiotensin converting enzyme

et al, 2015; Zinman et al, 2015; Marso et al, 2016; Neal et al, 2017; Wiviott et al, 2019) and in a RWE study of patients managed within a large integrated health system (Pantalone et al, 2015). Mean ages for patients in the four comorbidity cohorts (range, 67.5 [10.1]-72.1 [9.6] yr) were greater than the mean age for patients in the non-ASCVD cohort (60.6 [11.8] yr). Across the cohorts, up to one-half of patients were Caucasian, with up to one-third of patients with race unknown.

More patients lived in the South (cohort range, 45.2%-50.0%) than in other regions. Higher percentages of patients in the ASCVD, HF, and HF/CKD cohorts had a history of smoking (51.0%, 52.5%, and 47.2%, respectively) compared with the all-patient, non-ASCVD, and CKD cohorts (37.9%, 36.0%, and 39.9%). Mean BMIs (SDs) ranged from 32.1 (6.8) to 34.6 (8.1), exceeding the threshold for Class 1 obesity (BMI >30) and similar to values reported elsewhere (Scirica et al, 2013; White et al, 2013; Pfeffer et al, 2015; Zinman et al, 2015; Neal et al, 2017; Pantalone et al, 2017; Wiviott et al, 2019). Across the cohorts, mean (SD) systolic (range, 130.9 [17.3]-132.7 [17.7] mmHg) and diastolic (range, 72.9 [11.2]-77.7 [10.0] mmHg) blood pressure was similar at baseline. Approximately eight percent (8.1%) of all patients were hypertensive at baseline (i.e., BP ≥140/≥90 mmHg). Across the cohorts, the percentage of patients with written prescriptions for or documented use of anti-hypertensive medication was highest for angiotensin converting enzyme inhibitors (range, 49.6%55.7%), followed by angiotensin receptor blockers (range, 34.0%46.0%), thiazide diuretics (range, 34.2%-44.3%), calcium channel blockers (range, 12.0%-25.5%), and aldosterone receptor antagonists (2.6%-20.9%).

Complications

Microvascular complications were present in 17.5% of all patients, a percentage that aligns with findings from a claims-based RWE study (O'Brien et al, 2018). Percentages of patients with microvascular complications (nephropathy, neuropathy, and retinopathy) were greatest in the HF/CKD cohort (27.3%, 29.1%, and 6.7%, respectively) (ranges for the microvascular complications for other cohorts, 2.3%-22.8% [nephropathy], 7.9%20.7% [neuropathy], and 1.5%-5.5% [retinopathy]). Greater percentages of patients had evidence at baseline of albuminuria (UACR >30 mg/g) and renal dysfunction (eGFR <60 mL/min/1.73m^2) in the non-ASCVD (6.5% and 15.1%, respectively), ASCVD (9.9% and 22.3%), and HF (14.6% and 34.6%) cohorts than what was recorded for these groups using ICD-9 codes for nephropathy (non-ASCVD, 2.3%; ASCVD, 3.7%; and HF, 5.4%). Percentages of patients with macrovascular complications (myocardial infarction and stroke) were highest in the HF/CKD cohort (11.0% and 12.2%, respectively) (ranges for other cohorts, 0.8%-6.9% and 2.2%-8.9%).

Provider Specialty

Most patients (>90%) completed three or more visits to an HCP during the 12-month Baseline period, with the mean (SD) number of visits ranging from 7.0 (5.5) (non-ASCVD cohort) to 11.2 (8.5) (HF/CKD cohort) annually. Most patients (82.5%) received intensification prescriptions from HCPs in primary care practices (i.e., family medicine, internists, and primary care specialists) (range, 65.1% [non-ASCVD]-82.1% [HF/CKD]).

Comorbidities

A summary of comorbidities observed any time before Index is shown in **Table 3**. Across the cohorts, the most commonly occurring comorbidities (aside from defining comorbidities [100%]) were hyperlipidemia (including dyslipidemia and hypercholesterolemia) (range, 71.6%-83.3%), hypertension (34.1%-55.0%), and obesity (28.2%-39.0%). The cohort with the greatest percentage of patients with hypertension (55.0%) and with anemia (27.3%) was the HF/CKD cohort.

The overweight/obese phenotype appeared to occur more frequently in the HF, CKD, and HF/CKD cohorts than in the nonASCVD and ASCVD cohorts. A numerically greater percentage of patients in the ASCVD, CKD, and HF/CKD cohorts had a diagnosis of hyperlipidemia than patients in the non-ASCVD and HF cohorts.

TABLE 3 | Comorbidity Summary*

COMORBIDITY, N (% OF COHORT)	Patients with T2D					
	All N=27,501	non-ASCVD N=21,889	ASCVD N=1,665	HF N=756	CKD N=2,755	HF/CKD N=436
Atherosclerotic cardiovascular disease	2,500 (9.1)	0 (0)	1,665 (100)	179 (23.7)	497 (18.0)	159 (36.5)
Coronary artery disease	1,127 (4.1)	0 (0)	749 (45.0)	93 (12.3)	210 (7.6)	75 (17.2)
Cerebrovascular disease	179 (0.7)	0 (0)	124 (7.4)	8 (1.1)	39 (1.4)	8 (1.8)
Peripheral artery disease	1,383 (5.0)	0 (0)	880 (52.9)	102 (13.5)	298 (10.8)	103 (23.6)
Heart failure	1,192 (4.3)	0 (0)	0 (0)	756 (100)	0 (0)	436 (100)
Chronic kidney disease	3,191 (11.6)	0 (0)	0 (0)	0 (0)	2,755 (100)	436 (100)
Hyperlipidemia	20,253 (73.6)	15,667 (71.6)	1,377 (82.7)	564 (74.6)	2,294 (83.3)	351 (80.5)
Hypertension	10,065 (36.6)	7,472 (34.1)	766 (46.0)	305 (40.3)	1,282 (46.5)	240 (55.0)
Overweight/obese	8,251 (30.0)	6,424 (29.3)	469 (28.2)	265 (35.1)	923 (33.5)	170 (39.0)
Depression	3,332 (12.1)	2,558 (11.7)	260 (15.6)	116 (15.3)	341 (12.4)	57 (13.1)
Obstructive sleep apnea	2,403 (8.7)	1,754 (8.0)	177 (10.6)	111 (14.7)	285 (10.3)	76 (17.4)
Anemia	1,974 (7.2)	1,138 (5.2)	151 (9.1)	86 (11.4)	480 (17.4)	119 (27.3)
Liver disease, non-alcoholic	1,130 (4.1)	904 (4.1)	70 (4.2)	23 (3.0)	119 (4.3)	14 (3.2)
Chronic obstructive pulmonary disease	493 (1.8)	285 (1.3)	54 (3.2)	53 (7.0)	67 (2.4)	34 (7.8)
Angina (stable, unstable)	423 (1.5)	144 (0.7)	92 (5.5)	47 (6.2)	94 (3.4)	46 (10.6)

*Comorbidities were recorded at any time in a patient's history before Index.

Abbreviations: T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; HF=heart failure; CKD=chronic kidney disease.

Glucose-Lowering Drug Classes

Across the cohorts, a greater percentage of patients had documentation or written prescriptions for DPP-4 inhibitors (54.6%-60.8%) than for GLP-1 receptor agonists (range, 22.2%-25.7%) or for SGLT2 inhibitors (range, 16.5%-37.8%) (**Table 4**). For SGLT2 inhibitors, cohorts with the lowest percentages of patients with documentation or written prescriptions were the CKD (21.9%) and HF/CKD (16.5%) cohorts, with the highest percentage in the non-ASCVD (37.8%) cohort. Fewer than 2% of patients in each cohort had documentation or written prescriptions for combination DPP-4 inhibitor and SGLT2 inhibitor medications. The percentage of patients who had documentation or written prescriptions for two concurrent drugs from these three classes ranged from 19.0% to 25.7%, with numerically higher percentages shown for the non-ASCVD and the ASCVD cohorts. The percentage of patients with documentation or written prescriptions for concurrent

TABLE 4 | Prescription Glucose-Lowering Medication Summary*

MEDICATION SUMMARY, N (% OF COHORT)	Patients with T2D					
	All N=27,501	non- ASCVD N=21,889	ASCVD N=1,665	HF N=756	CKD N=2755	HF/CKD N=436
Dipeptidyl peptidase-4 inhibitors	15,267 (55.5)	11,955 (54.6)	969 (58.2)	415 (54.9)	1,676 (60.8)	252 (57.8)
Glucagon-like peptide-1 receptor agonists	6,947 (25.3)	5,635 (25.7)	415 (24.9)	175 (23.1)	611 (22.2)	111 (25.5)
Sodium-glucose cotransporter-2 inhibitors	9,702 (35.3)	8,272 (37.8)	561 (33.7)	193 (25.5)	604 (21.9)	72 (16.5)
DPP-4 inhibitor and SGLT2 Inhibitor combo meds	476 (1.7)	413 (1.9)	25 (1.5)	7 (0.9)	29 (1.1)	2 (0.5)
Two concurrent from the following: DPP-4i, GLP-1 RA, or SGLT2i	6,815 (24.8)	5,615 (25.7)	410 (24.6)	155 (20.5)	552 (20.0)	83 (19)
Three concurrent of the following: DPP-4i, GLP-1 RA, and SGLT2i	3,161 (11.5)	2,660 (12.2)	186 (11.2)	60 (7.9)	222 (8.1)	33 (7.6)
Insulin/Insulin analogs	10,762 (39.1)	7,970 (36.4)	764 (45.9)	375 (49.6)	1,398 (50.7)	255 (58.5)
Sulfonylureas	10,191 (37.1)	7,995 (36.5)	655 (39.3)	268 (35.4)	1,099 (39.9)	174 (39.9)
Thiazolidinediones	4,359 (15.9)	3,360 (15.4)	266 (16)	99 (13.1)	563 (20.4)	71 (16.3)

*Documentation or written prescriptions for medications occurred at any time in a patient's history before and including Index.

Abbreviations: T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; HF=heart failure; CKD=chronic kidney disease; SGLT2i=sodium-glucose cotransporter 2 inhibitor; GLP-1 RA=glucagon-like peptide 1 receptor agonist; DPP-4i=dipeptidyl peptidase 4 inhibitor.

prescriptions for DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors ranged from 7.6% to 12.2%. Percentages of patients with documentation or written prescriptions for insulin or insulin analogs in the concordant comorbidity cohorts (range, 45.9%-58.5%) were higher than that shown for the non-ASCVD cohort (36.4%). Percentages of patients with documentation or written prescriptions for sulfonylureas were similar across the cohorts (range, 35.4%39.9%). The highest and lowest percentages of patients with documentation or written prescriptions for thiazolidinediones occurred in the CKD (20.4%) and the HF (13.1%) cohorts, respectively.

TABLE 5 | Glycated Hemoglobin Before and After Treatment Intensification

	Patients with T2D					
HbA1c*	**All** N=27,501	**non-ASCVD** N=21,889	**ASCVD** N=1,665	**HF** N=756	**CKD** N=2,755	**HF/CKD** N=436
Patients with Baseline HbA1c, n (%)	27,501 (100)	21,889 (100)	1,665 (100)	756 (100)	2,755 (100)	436 (100)
Mean HbA1c, (SD)	8.5 (4.1)	8.5 (4.4)	8.3 (1.7)	8.4 (1.8)	8.3 (4.1)	8.1 (1.8)
<7.0%	5,715 (20.8)	4,394 (20.1)	351 (21.1)	181 (23.9)	669 (24.3)	120 (27.5)
7.0%-7.9%	7,286 (26.5)	5,817 (26.6)	439 (26.4)	180 (23.8)	752 (27.3)	98 (22.5)
8.0%-8.9%	5,882 (21.4)	4,630 (21.2)	382 (22.9)	160 (21.2)	612 (22.2)	98 (22.5)
>9.0%	8618 (31.3)	7,048 (32.2)	493 (29.6)	235 (31.1)	722 (26.2)	120 (27.5)
Patients with Follow-up HbA1c, (%)	(100)	(100)	(100)	(100)	100	(100)
Mean HbA1c, (SD)	8.0 (4.7)	8.0 (3.6)	8.0 (4.5)	8.0 (1.8)	8.1 (10.1)	7.7 (1.6)
<7.0%	9,291 (33.8)	7,298 (33.3)	579 (34.8)	256 (33.9)	990 (35.9)	168 (38.5)
7.0%-7.9%	7,436 (27.0)	5,952 (27.2)	440 (26.4)	179 (23.7)	761 (27.6)	104 (23.9)
8.0%-8.9%	4,703 (17.1)	3,740 (17.1)	292 (17.5)	138 (18.3)	453 (16.4)	80 (18.3)
>9.0%	6,071 (22.1)	4,899 (22.4)	354 (21.3)	183 (24.2)	551 (20.0)	84 (19.3)

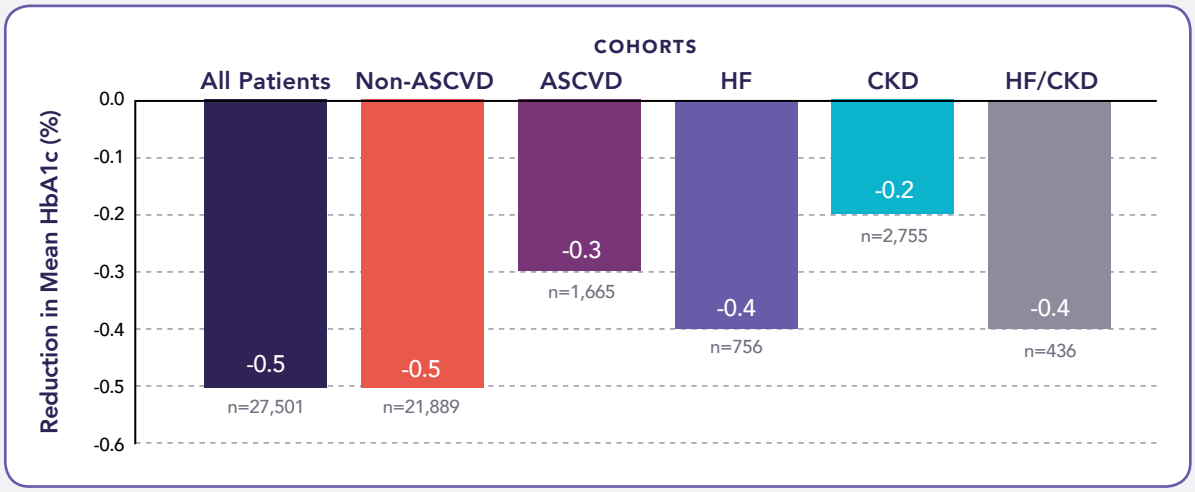
*HbA1c=glycosylated hemoglobin reported as percent (%) of total hemoglobin.

Abbreviations: T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; HF=heart failure; CKD=chronic kidney disease; SD=standard deviation.

Treatment Intensification

HbA1c levels are strongly correlated with microvascular complications, and their measurement is the primary means of assessing longitudinal glycemic control for diabetes care (ADA, 2019g).

FIGURE 3 | Change in Glycated Hemoglobin Following Treatment Intensification*



*Reduction in mean HbA1c was calculated as the difference between the first mean HbA1c after Index and the last mean HbA1c before Index.

Abbreviations: ASCVD=atherosclerotic cardiovascular disease; HF=heart failure; CKD=chronic kidney disease; HbA1c= glycosylated hemoglobin reported as percent (%) of total hemoglobin.

Mean (SD) HbA1c levels at baseline were similar across the comorbidity cohorts (range, 8.1 [1.8]-8.5 [4.4]) and higher than the lowest target level (HbA1c <7.0%) (**Table 5**). Following treatment intensification, reductions in mean HbA1c were observed across the cohorts (range, 7.7 [1.6]-8.1 [10.1]). In all cohorts, intensification was associated with greater percentages of patients achieving HbA1c values of less than 7%.

Reductions in mean HbA1c from baseline were 0.5% for the all-patient and non-ASCVD (without HF or CKD) cohorts, 0.3% for the ASCVD cohort, 0.4% for the HF cohort, 0.2% for the CKD cohort, and 0.4% for the HF/CKD cohort (**Figure 3**).

DISCUSSION

Specific goals of T2D management include prevention or delay of complications and improvement in QoL, both accomplished through glycemic control and risk factor management. The complexity of interactions between T2D, concordant comorbidities, and ensuing complications requires a coordinated approach that manages risk while maintaining guideline-specified therapeutic targets. With the addition of new drug classes and an emphasis on self-management and shared decision-making, more patients are achieving individualized treatment goals. However, many patients struggle to meet targets for glycemic control or reduced cardiovascular risk.

The cohort analysis and case study demonstrate how de-identified ambulatory patient data from an EHR platform, in this instance Practice Fusion from Veradigm, may be leveraged to derive meaningful and actionable RWE. The study identified the HF/CKD cohort as having a greater incidence of microvascular and macrovascular complications than other comorbidity cohorts, with more visits annually to HCPs, findings that speak to the challenges of multi-morbidity in T2D. Although mean BMI values indicated all cohorts exceeded the threshold for Class 1 obesity (BMI >30), the overweight/obese phenotype, established using ICD-9 codes, appeared to occur more frequently in the HF, CKD, and HF/CKD cohorts. Across the cohorts, treatment intensification with glucose-lowering agents from six drug classes was associated with more patients achieving HbA1c values of less than 7%. This study further suggests opportunities may exist for consideration of glucose-lowering drug classes with strong evidence of cardiovascular risk reduction and possibly nephro-protective effects to address unmet needs.

Evolving natural language processing (NLP) background capability may enable efficient and consistent capture of multiple data elements stored within free text on EHR platforms. Such data may be embedded in provider notes, consultation notes and discharge summaries, and descriptive reports associated with medical testing. In the present study, HbA1c values were captured as Logical Observation Identifier Names and Codes (LOINC) system codes and values in structured laboratory results and unstructured laboratory result descriptions. Forty-one percent (41%) of HbA1c values were supplemented through NLP enhancement.

As platforms that manage comprehensive health information from individual patients, EHRs have the potential to assist HCPs in care coordination and in providing patient support. Cloud-based, digital health information systems such as Practice Fusion that collect RWD communicate bidirectionally, and insights arising from longitudinal analyses of medication use, laboratory values, and patient-reported outcomes may be offered to HCPs at the point-of-care. Informed as to how a patient's progress may align with care plan goals and treatment guidelines, HCPs may offer recommendations for adjustments to therapy and lifestyle to enable shared decision-making for implementing individualized care management. For patient self-management, a critical component of T2D care plans, cloud-based provider-patient portals on the web and in mobile applications that interface with EHRs may deliver educational content from HCPs that builds awareness of the benefits of treatment intensification and risks associated with concordant comorbidities. For patients who are not achieving evidence-based goals, clinical support for reassessment and treatment modification may be offered to incorporate newly developed patient factors and to minimize risks of therapeutic inertia (ADA, 2019a, ADA, 2019e).

Interactive EHR platforms have the potential to support T2D patient care and therapeutic outcomes in a variety of real-world scenarios. In the present study, three cohorts (non-ASCVD, ASCVD, and HF) had greater percentages of patients with evidence of albuminuria and renal dysfunction than what was recorded for these groups using ICD-9 codes for nephropathy, suggesting a need for longitudinal assessment of UACR and eGFR. Computer algorithms embedded in EHR platforms may be used to monitor laboratory values occurring outside of normal ranges and to offer tools for clinical support to enable accurate diagnosis and implementation of evidence-based, guideline-recommended adjustments to care plans. EHR tools may also be used to inform provider and patient decisions regarding glucose and systolic blood pressure control, as was done in a community-based, randomized trial of patients with T2D (O'Connor et al, 2011). To coordinate

care across multiple disciplines, EHRs may be used to electronically cross reference association guidelines to create patient-specific plans that take into account concordant and discordant comorbidities (Magnan et al, 2015). Health plans may be advised of at-risk members who might benefit from lifestyle changes or care discussions with their HCPs.

Inconsistencies in patient care quality across provider settings suggest system-level improvements may be warranted to enable healthcare delivery teams and empower patients. As clinical information systems in coordinated chronic care models, registries have been endorsed by the ADA as a means of providing patient-specific and population-based support to diabetes care teams (Davies et al, 2018; ADA, 2019c). Additional insights regarding the care and safety of patients with T2D may be gained by interfacing EHRs with established diabetes-specific registries (NIDDK, 2019). As real-world, observational studies, registries seek patient data across large, generalizable populations to gain an understanding of treatment effectiveness and safety outcomes associated with longitudinal adjustments in clinical management (Gliklich et al, 2014). Interfaced EHR platforms may host case record forms for uniform data capture by registries and facilitate recruiting by identifying providers with eligible patients to continually populate the registry. In post-approval environments, EHRs have the potential to support educational initiatives and communication plans intended to mitigate risks associated with disease, multi-morbidity, or therapies, for the benefit of both providers and patients. With a commitment to interoperability standards and certification for meaningful use, Veradigm is working to enable registries through RWD and real-world evidence (RWE) derived from RWD available on its EHR platforms.

As complementary to data obtained from RCTs, RWE may inform drug development according to the FDA's Real-World Evidence Program, a framework intended to facilitate cost-effective, efficient support for additional indications for approved drugs, and possibly other post-approval regulatory action (Sherman et al, 2016; FDA, 2018). In keeping with aims outlined by the FDA, RWD and RWE from registries and other observational studies, medical claims, and EHRs have the potential to be leveraged across the entire life cycle of drug research and development, from discovery and pre-clinical efforts (helping to establish burden of disease and to generate hypotheses) through clinical development (informing trial design, feasibility, and study criteria; enabling patient recruitment), regulatory authorization (accelerating approval with commitment for observational studies), market access (comparing effectiveness, resource utilization, and cost outcomes), and post-approval (assessing pharmacovigilance; expanding indications, dosing, and populations not previously studied; tracking compliance and adherence) (Sherman et al, 2016; FDA, 2018).

CONCLUSION

Electronic health platforms have the potential to enable clinical support and inform medical innovation and drug development. A cohort analysis and case study using de-identified RWD from an EHR platform Practice Fusion, a Veradigm offering, demonstrates how RWE may offer insight regarding the impact of concordant morbidities in T2D. Future studies that leverage RWE from electronic health platforms may provide additional insight in support of individualized diabetes management plans.

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