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Brief title	Educational Intervention to Increase Select Guideline-recommended Cardioprotective Medications in Patients With Diabetes
Official title	Improving Outcomes in Patients With Comorbid T2DM and ASCVD: Population Health Management Interventions Supporting Guideline-recommended SGLT2i and GLP-1 RA Medications
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TABLE OF CONTENTS

BACKGROUND AND RATIONALE

Over 34 million individuals in the United States in 2018 were estimated to have diabetes (diagnosed and undiagnosed), with approximately 95% of those individuals having type 2 diabetes mellitus (T2DM).[1] Diabetes increases the risk of developing cardiovascular disease (CVD) and nearly doubles the risk of death from heart disease or stroke.[2] While CVD is associated with morbidity and mortality in patients with T2DM, the economic impact is also substantial. The median annual healthcare costs per patient with CVD and T2DM has been estimated to be 112% higher compared to patients with T2DM without CVD, hospitalizations driving the costs.[3]

While there are evidence-based and guideline-recommended therapies for patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) that reduce morbidity and mortality associated with CVD, gaps in treatments exist. Specifically, utilization of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1 RA) medications with proven cardiovascular benefit remains low (<10%),[4] despite guideline recommendations from the American Diabetes Association (ADA) and American College of Cardiology (ACC) supporting their use.[5,6] Currently, the products with Food and Drug Administration (FDA) approved/labeled cardiovascular specifically in patients with ASCVD benefit include SGLT2is empagliflozin, canagliflozin, and dapagliflozin, and GLP-1 RAs dulaglutide, liraglutide and injectable semaglutide.

A Pharmacy Quality Alliance (PQA) measure titled, "Use of Medications to Prevent Major Cardiovascular Events in Persons with Diabetes (CVDM)", was voted on and approved by the membership in December 2020, is another strategy to help address this noted gap in effective care. However, complementary evidence-based initiatives are needed to communicate benefits of these medications to providers while simultaneously encouraging patients to engage in discussions with providers about their CV risk and ways to reduce future events.

As such, the purpose of this collaborative pilot is to test the impact of a dual educational intervention that includes communication to providers that their identified patients with T2DM and existing ASCVD may be candidates for guideline recommended medications, combined with communication to the identified at-risk patients regarding their CV risk.

STUDY METHODS

Study Objectives

The underutilization of ADA and ACC recommended treatments, specifically SGLT2i and GLP-1 RA medications with CV benefit, have been identified in the literature. In an effort to close this gap in the high-risk population of patients with T2DM and ASCVD, this pilot aims to inform select providers about the recent updates in guidelines regarding optimal treatment and also aims to inform patients about their risk and encourage discussions with providers about how to reduce their future risk of CV events.

Primary Objective

- Evaluate the impact of a dual educational outreach on 6-month frequency of SGLT2i and GLP-1 RA medication initiation by comparing patients and providers who receive and who do not receive the intervention.

Secondary Objectives

- Evaluate the impact of a dual educational outreach on 12-month frequency of SGLT2i and GLP-1 RA medication initiation by comparing patients and providers who receive and who do not receive the intervention.

- Evaluate the adherence and persistence to SGLT2i and GLP-1 RA medications 6-months after initiation. (Note: this outcome may also be assessed at 12-months post-initiation based on results of 6-month measure)

The hypothesis is that there will be a significantly greater (2% absolute increase) initiation of SGLT2i and GLP-1 RA medications with CV benefit among those who receive the educational outreach and message as compared to those who do not receive the intervention.

Data Source

The data source will be Humana's Research Database (Louisville, KY), which contains claims data for all of Humana's fully-insured commercial and Medicare membership. The data for this study include member enrollment, medical, pharmacy and lab results data.

Study Design

The study will be a cluster randomized design of an educational intervention versus no intervention, stratified by value-based arrangement (value based or non-value-based). Eligible patients and providers, based on the inclusion and exclusion criteria, will be identified via administrative medical and pharmacy claims. Patients enrolled in Medicare Advantage Prescription Drug (MAPD) plans, excluding those who are dually eligible for Medicaid, in the

East region (Kentucky, Pennsylvania, West Virginia, 6 counties in south New Jersey) will be required to have an indication of T2DM and ASCVD (coronary artery disease, cerebrovascular disease, peripheral arterial disease of atherosclerotic origin) in addition to 12 months of pre-identification continuous enrollment. These patients must not be currently or recently been treated with one of the SGLT2i or GLP-1 RA medications.

A sample of patients and their attributed primary care providers from the identified eligible cohort will be identified. Primary care providers will be identified as a value-based care provider or a non-value-based care provider.

- Providers in non-value based arrangements include those in fee-for-service arrangements and those in the Star quality recognition program. Providers are automatically enrolled in the Star program if the practice has >30 Humana patients. As such, those providers aren't considered to be in a value-based arrangement since this program enrollment is by default.
- Providers in value-based arrangements include those in path-to-value or full value contracts.
    - Path-to-value arrangements are engaged in model practice, medical home, and/or shared savings arrangements. Practices in these arrangements typically have the opportunity to share in any monetary incentive by effectively managing costs and revenue, but are not at risk for owing a deficit as in a downside arrangement.
    - Practices in full value arrangements assume a certain proportion of risk for costs that exceed the premium (based on the proportion of risk assumed for Medicare Part A and B costs). However, the incentive opportunity is typically more substantial than that of practices in other programs.

Primary care providers will be randomized, stratified by value-based and non-value based, into the intervention and control groups. All eligible patients of the primary care provider randomly sampled will be included in the study. For the intervention, the attributed primary care provider (e.g., family practice, general practice, internal medicine, geriatricians, nurse practitioners, physician assistants) and specialists (e.g., cardiologists, endocrinologists) will be contacted. Specialist providers of interest (i.e., cardiology and endocrinology) will be identified for specific patients based on recent claims with evidence of that patient's visit to that provider and outreach will also be conducted to those specialists. The contact information for those who will be receiving the outreach will be provided to a Humana approved third party vendor. The vendor will first send a direct mail letter or fax to the attributed primary care provider and the specialists, as able to be identified, that highlights the guideline-recommendations from the ADA and ACC regarding use of SGLT2i and/or GLP-1 RA medications for patients with T2DM and ASCVD. This mailing or fax to all applicable providers will also include the names of the patients identified who may be eligible for this treatment. It will be noted in each communication that the primary care and specialist providers that have been identified as providing care for the patient will be sent the communication, as well, and the names of those providers will be furnished in the communication. In the event the available fax number results in a failed fax attempt, a mailing will be sent instead. Patients will also be sent a direct mail letter by a Humana contracted third party vendor that will explain their CV risk, provide resources to understand their risk (e.g., ADA Know Diabetes By

Heart), and encouraging discussion with their providers about strategies (including medical, pharmacological and lifestyle) to reduce their risk for future CV-related events.

After the mailing (or fax) has been sent, a follow-up call to providers and patients will be conducted to ensure the message was received, reiterate the content of the initial outreach, and encourage discussions between patients and providers about CV risk reduction strategies. This call will be planned to take place within a few weeks (~3 weeks) from the initial mailing. While it will be requested to speak directly with the provider, nurses or other office staff may receive the call. Up to three call attempts will be made, with general messages being left asking for a return call if a voicemail is reached.

Three months after the initial outreach, another mailed/faxed communication will be sent to the providers reiterating the messaging from the first two communications, and including the list of patients who are still eligible for treatment and also noting those who have received treatment. The patients will also receive another direct mail communication approximately 3 months after the initial outreach reiterating the messaging from the first two communications.

The primary outcome for this study is the initiation of guideline-recommended SGLT2i or GLP-1 RA medications with CV benefit (excluding combination products) within 6-months of the initial outreach. Secondary outcomes include: 1) initiation of the medications of interest (excluding combination products) within 12 months of the initial outreach; 2) initiation of guideline-recommended SGLT2i or GLP-1 RA medications with CV benefit (including combination products) within 6-months of the initial outreach; 3) initiation of guideline-recommended SGLT2i or GLP-1 RA medications with CV benefit (including combination products) within 12-months of the initial outreach; and 4) adherence to SGLT2i or GLP-1 RA medications 6-months post-initiation; and 5) persistence to SGLT2i or GLP-1 RA medications 6-months post-initiation.

Identification and randomization: July 2021 (date on which data extraction begins)

Index event: date of first outreach to patients/providers (August 2021)

Second outreach (calls): start 3 weeks post-index

Third outreach (mailing/fax): starts 3 months post-index

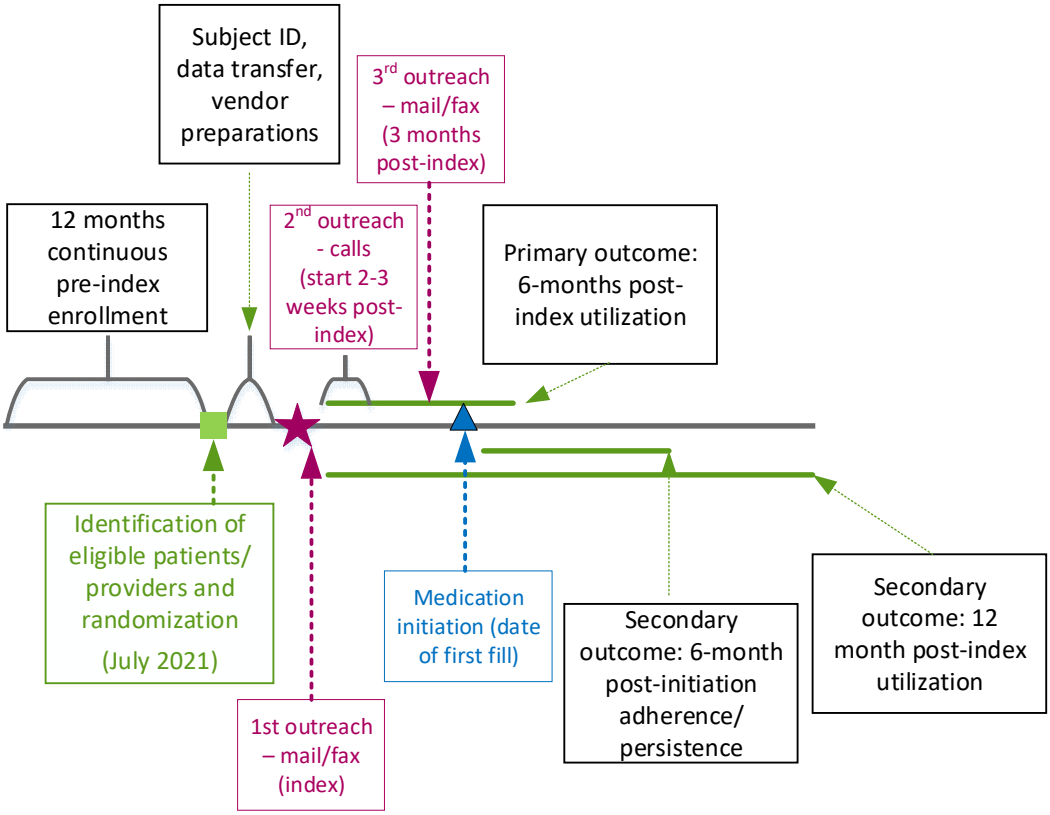
Pre-identification and pre-index: 12-months continuous enrollment

Post-index: none

Follow-up: the primary outcome will be evaluated at 6-months and a secondary outcome will be utilization at 12 months post-index

Full data period: up to 2 years pre-index to 12-months post-index (July 2019 – August 2022)

Figure. Study design



The inclusion and exclusion criteria, below, will be utilized to identify the eligible patient population.

Patient

- Patients with T2DM defined as ≥2 outpatient diagnoses of T2DM in any position on separate days; OR ≥1 inpatient diagnosis T2DM in any position; OR ≥1 outpatient diagnosis in any position AND ≥1 medication claim for T2DM
- ≥1 diagnosis code for ASCVD (coronary artery disease diagnoses or procedures, cerebrovascular disease, peripheral artery disease of atherosclerotic origin) on any claim type in any position within the 24-month period prior to identification
- Enrolled in a Humana Medicare Advantage Prescription Drug plan with ≥12 months pre-identification continuous enrollment (no more than a 31 day gap) as of the identification date and currently enrolled as of the identification date
- Age 18-85 years at time of identification
- Patients residing in Kentucky (KY), West Virginia (WV), Pennsylvania (PA), and 6 counties in south New Jersey (NJ) (Burlington, Camden, Cumberland, Gloucester, Mercer, Salem) (United States)

Provider

- Primary care providers of the identified patients

Exclusion Criteria:

Patients

- ≥1 diagnosis or procedure code for end-stage kidney disease, renal transplant, dialysis or kidney failure
- Any hospice or long-term care residence
- ≥1 code for pregnancy/childbirth
- Patients with any use of SGLT2i or GLP-1 RA medications in the pre-identification period
- Patients without an attributed primary care provider
- Patients on do not contact lists
- Patients without valid addresses and telephone numbers
- Patients with ≥1 diagnosis for type 1 diabetes pre-identification

Primary care providers

- Providers on do not contact lists
- Providers without valid fax/mailing address and phone number
- Providers with <3 and >50 eligible patients
- Providers with eligible patients across multiple risk arrangements

Specialist providers will be included in the outreach if there is an indication from the claims data that the identified patient has had an encounter with a cardiologist and/or endocrinologist up to 24-months pre-identification. These providers will not be contacted if on do not contact lists or if there are no valid fax/mailing address and phone numbers for those providers. Only specialist providers with <50 eligible patients will be included.

Among those primary care providers and patients eligible for the study, a simple, random sample of primary care providers will be selected to be included for the intervention and control groups. All eligible patients of the randomly selected providers will be included in the same treatment arm (i.e., no cross over of patients into intervention or control arms). Providers and their patients assigned to the intervention arm will be compared to the randomly assigned providers and patients who will not be receiving any educational outreach or messaging.

This study will utilize data from patients enrolled in a US Medicare Advantage plan, so the results may not be generalizable for younger patients in commercial plans or patients outside of the US. In addition, these data are from patients who have elected enrollment into one US plan (Humana), thus generalizability to other health plans or the US population of patients with T2DM and ASCVD may be limited. The inclusion/exclusion criteria are constructed to attempt to include the broadest sample of patients who could be eligible to receive this type of therapy.

Measures

Exposure

Intervention Group

Patients and providers receiving the educational outreach and messaging will be in the intervention group. There will be three rounds of outreach for patients and providers.

- Patients
    - Outreach 1: The first outreach will be a direct mailing to patients that will explain their CV risk, provide resources to understand their risk (e.g., ADA Know Diabetes By Heart), and encouraging discussion with their providers about strategies (including medical, pharmacological and lifestyle) to reduce their risk for future CV-related events.
    - Outreach 2: The second outreach will be a telephone call to patients that will reiterate the message in the letter that will take place approximately 3 weeks after the initial mailing was sent. Up to three call attempts will be made, with general messages being left asking for a return call if a voicemail is reached.
    - Outreach 3: The last outreach will be a direct mailing to patients reiterating the messages in the first two outreach attempts that will take place approximately 3 months after the initial mailing was sent.
- Providers
    - Outreach 1: The first outreach to providers will be a fax or direct mailing to the primary care provider and specialist providers (endocrinologist or cardiologist). Fax will be the first and preferred method of communication. However, if the fax fails or if there is not a valid fax number on file, direct mail will be used. The communication will highlight the guideline-recommendations from the ADA and ACC regarding use of SGLT2i and/or GLP-1 RA medications for patients with T2DM and ASCVD. This mailing or fax to all applicable providers will also include the names and date of birth of the patients identified who may be eligible for this treatment. It will be noted in each communication that the primary care and specialist providers that have been identified as providing care for the patient will be sent the communication, as well, and the names of those providers will be furnished in the communication.
    - Outreach 2: The second outreach will be a telephone call to providers that will reiterate the message in the letter that will take place approximately 3 weeks after the initial mailing/fax was sent. While it will be requested to speak directly with the provider, nurses or other office staff may receive the call. Up to three call attempts will be made, with general messages being left asking for a return call if a voicemail is reached.
    - Outreach 3: Three months after the initial outreach, another mailed/faxed communication will be sent to the providers reiterating the messaging from the first two communications, and including the list of patients who are still eligible for treatment and also noting those who have received treatment.

Control Group

This will include the patients meeting the inclusion/exclusion criteria and their providers who were randomized to not receive the educational outreach and messaging.

Primary Outcome Measure:

1. Guideline-based SGLT2i or GLP-1 RA medication initiation (excluding combination products) [Time Frame: 6-months] Proportion of patients who have ≥1 pharmacy claim for SGLT2i or GLP-1 RA medications with cardiovascular benefit (excluding combination products)

Secondary Outcome Measures:

1. Guideline-based SGLT2i or GLP-1 RA medication initiation (excluding combination products) [Time Frame: 12-months]: Proportion of patients who have ≥1 pharmacy claim for SGLT2i or GLP-1 RA medications with cardiovascular benefit (excluding combination products)

2. Adherence and persistence to guideline-based SGLT2i or GLP-1 RA medications [Time Frame: 6-months] Adherence and persistence to SGLT2i or GLP-1 RA medications with cardiovascular benefit (excluding combination products)

3. Guideline-based SGLT2i or GLP-1 RA medication initiation (including combination products) [Time Frame: 6-months]: Proportion of patients who have ≥1 pharmacy claim for SGLT2i or GLP-1 RA medications with cardiovascular benefit (including combination products)

4. Guideline-based SGLT2i or GLP-1 RA medication initiation (including combination products) [Time Frame: 12-months]: Proportion of patients who have ≥1 pharmacy claim for SGLT2i or GLP-1 RA medications with cardiovascular benefit (including combination products)

Baseline covariates:

- Demographics
    - Age
    - Sex
    - Race (as available; Black, White, other, unknown/missing)
    - Population density (e.g., rural, urban, suburban)
    - Chronic special needs plan enrollment (as available)
- Clinical characteristics
    - Elixhauser comorbidity index (based on medical claims)[7-9]
    - RxRisk V (comorbidity index based on medications as proxy)[10]
    - Prior MI, stroke, revascularizations
    - Number of unique medications
    - Use and type of antihyperglycemic medications (by class)
    - Use and type of cardiovascular medications (by class)
    - Indication of prior or current tobacco use
    - Indication of obesity and/or body mass index (BMI)

- Laboratory values (as available) (cholesterol, HbA1c, serum creatinine)

- All-cause healthcare resource utilization
  - Inpatient hospitalization
  - Total length of stay for hospitalizations
  - Emergency department visits
  - Provider encounters
  - Other outpatient visits (procedures, tests, imaging, durable medical equipment, other services, and unclassified)
- All-cause costs

Provider characteristics

- Value-based care arrangement for primary care providers
- Provider information (e.g., practice size, as available)

Statistical Analysis Plan

Primary Objective

Evaluate the impact of a dual educational outreach on 6-month frequency of SGLT2i and GLP-1 RA medication initiation by comparing patients and providers who receive and who do not receive the intervention.

The eligible patients and providers will be identified based on the inclusion/exclusion criteria. The attributed providers for each patient will be identified. For the primary care providers, the risk arrangement in which they are currently contracted, will be identified. Providers will be equally randomized via a simple random sample across (stratified) non-value based (e.g., fee-for service) or value-based (i.e., path-to-value and full value) arrangements between the intervention and control arms. All of the eligible patients for each identified primary care provider will be included in the same study cohort (i.e., either all control or all intervention).

Demographic, clinical and socioeconomic characteristics in the 12-month baseline period for patients and providers will be described (n (%), mean [standard deviation (SD)], median [interquartile range (IQR)], minimum, maximum). To ensure representativeness of the randomized sample, the sample will be compared to that of the sampling frame using standardized differences. The comparability between the intervention and control arms will also be assessed with standardized differences. Standardized differences will be assessed for each variable using the following example formulae[11]:

Continuous variables:

$$\frac{d = \bar{X}_{group1} - \bar{X}_{group2+3}}{\frac{\sqrt{s^2 group1 + s^2 group2 + 3}}{2}}$$

Binary variables:

$$\frac{d = \hat{p}_{group1} - \hat{p}_{group2+3}}{\frac{\sqrt{\hat{p}_{group1(1-\hat{p}_{group1})} + \hat{p}_{group2+3(1-\hat{p}_{group2+3})}}}{2}}$$

where $\overline{X}$ represents the mean of the covariate, s^2 represents the sample variance of $\overline{X}$, and $\hat{p}$ represents the prevalence of that covariate. Variables with a standardized difference less than 0.1 will be considered balanced.

The primary analytic cohort for this aim will consist of the patients/providers randomized to the control arm and the patients/providers randomized to the intervention arm who received at least the first outreach (i.e., no returned mailings/faxes).

The proportion of patients filling at least one pharmacy prescription for a SGLT2i or GLP-1 RA medication with CV benefit within 6-months of the intervention initiation will be compared. The unadjusted proportion of patients initiating the medications in each arm will be described (n [%]). A generalized linear mixed model (GLMM) with a binomial distribution and logit link will then be used to account for the clustering of patients within providers without any adjustment for covariates, except the stratification variable (random cluster effects).[12-14] Parameter estimates, odds ratios (ORs), standard error, 95% confidence intervals (CI) and p-values will be reported. If significant differences are detected between the patients in the intervention and control groups, greater than 0.1 in standardized difference, then adjustment for confounding, to minimize bias, utilizing regression models would be required as an additional analysis (e.g., covariate adjustment). For categorical variables with missing values, a missing category will be added. For continuous variables with missing values, the values will be categorized with a missing category added. This will allow for all patients to be retained in the analyses. No imputation will be conducted.

Secondary Objectives

Evaluate the impact of a dual educational outreach on 12-month frequency of SGLT2i and GLP-1 RA medication initiation by comparing patients and providers who receive and who do not receive the intervention.

The 12-month frequency of the SGLT2i and GLP-1 RA medication initiation with CV

benefit will be assessed using the same analytic cohorts and methodologies, as described above.

Evaluate the adherence and persistence to SGLT2i and GLP-1 RA medications 6-months after initiation.

The adherence and persistence among those initiating SGLT2i and GLP-1 RA medications 6-months after the first medication fill will be described. Adherence to either class of medication will be measured as proportion of days covered [PDC] among those initiating treatment. The PDC will be the days' supply of medication divided by the number of days total in the follow-up. This will be described as a continuous measure (mean (SD), median (IQR), range) as well as categorically (e.g., ≥80% and <80% or other categorizations as appropriate). Persistence to the index medications will be defined as non-discontinuation of the treatment. A patient will be considered non-persistent if there is a >90 day gap in therapy and persistent if there are no gaps in therapy or gaps in therapy of ≤90 days. Adherence and persistence may also be assessed at 12-months post-initiation based on results of 6-month measure.

Limitations

- Generalizability will be limited to the Humana MAPD population in the East region. However, the insights from this pilot may be used to inform and scale similar endeavors to other regions or populations.
- We cannot determine instances where a physician prescribed a treatment but the patient did not fill it (and why) or if a patient filled a prescription outside the data sources available to Humana (misclassification bias). Additionally, if patients do not stay enrolled in the health plan through the outcome observation period, then their outcomes may be misclassified as their data would not be available to capture. However, sensitivity analyses are planned to attempt to assess the impact of this bias.
- There may be barriers for providers to prescribe and/or patients to initiate and/or adhere to treatment, including factors related to increased member costs, not able to be ascertained from claims.
- Potential early adoption of an approved PQA measure linked with a risk arrangement in the region may impact outcomes. The study will randomize among patients and providers in different risk arrangements at the outset of the study and plan to conduct a subgroup analysis across arrangements.
- There may be additional forms of bias introduced to the study. While randomization at the provider level will be conducted to reduce selection bias, there may be other opportunities for this to occur. For example, we are only including patients who have attributed primary care providers, meaning they have received some type of ongoing care. Thus, these patients may be more activated with their health. Unmeasured confounding may be present due to some clinical data not able to be ascertained via an administrative claims database.

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