COVER PAGE

Title: Reducing Treatment Risk in Older Patients With Diabetes: Comparative Effectiveness of Academic Detailing With and Without Pre-Visit Patient Preparation

ClinicalTrials.Gov Registration: NCT04585191

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RETRO RCT Analytic Plan

Background

Over one-quarter of people aged 65 and older have type 2 diabetes, and this proportion is expected to increase rapidly in coming decades. Glycemic control in older patients must balance the short-term risks of treatment (e.g., hypoglycemia and its immediate consequences) with the long-term benefits of reduced microvascular complications (e.g., diabetic retinopathy or renal disease). Of increasing concern, hypoglycemia has become the leading preventable complication of treatment in this older population and increases the risk of cognitive decline, falls, lower health-related quality of life, hospitalization, and death. These severe consequences of hypoglycemia begin to change the balance between treatment benefit and risk as patients get older and develop increasing frailty and additional co-morbid chronic conditions. As patients age, they are less likely to experience the long-delayed benefits associated with tight glycemic control and more likely to suffer from the short-term risk of treatment-related hypoglycemia. This changing balance creates a critically important decisional dilemma of how best to balance long-term treatment goals with short-term treatment risks to optimize current health and well-being.

Design and Methods

We will conduct a comparative effectiveness randomized clinical trial involving the following two strategies for changing clinical management, both of which are transportable to a wide range of clinical settings and can be readily adopted into clinical practice:

1. **Academic detailing** is a well-validated strategy for changing prescribing practices that employs focused and pragmatic education for practicing clinicians. Academic detailing sessions are generally brief (30-45 minutes), integrated into the usual workday (e.g. during practice weekly meetings or lunches), and consist of clearly presented summaries of current evidence and guideline recommendations.
2. **Patient pre-visit preparation** is a more patient-centric strategy that has shown efficacy for improving clinical interactions and shared decision making. In this strategy, patients are prepared for clinical encounters prior to visits. Information exchange is bi-directional (i.e., patients receive information about relevant trade-offs and provide information about preferences and other relevant information to facilitate collaborative decision making with their provider).

The study has the following aims and design:

Aim 1: To compare academic detailing alone (Arm 1) to academic detailing + patient pre-visit preparation (Arm 2). We will measures differences in medication de-prescribing rates among well-controlled older patients with type 2 diabetes at high risk for medication-related hypoglycemia. [primary clinical outcome]

Aim 2: To compare differences between these 2 arms in patient-reported diabetes distress, decisional confidence, and perceived quality of care. [primary patient-reported outcomes]

Protocol Summary

Importance: Medication-related hypoglycemia is the leading cause of iatrogenic complications among older adults with type 2 diabetes (T2D).

Objective: Compare two strategies for insulin and/or sulfonylureas deprescribing in older patients with T2D treated in a PCP-randomized clinical trial (RCT).

Interventions: PCPs will 1+ academic detailing (AD) sessions that provide evidence to support diabetes medication reassessment and potential deprescribing strategies in older patients with T2D. Prior to their visit with a participating PCP, trial patients will be randomly assigned to receive either a pre-visit deprescribing activation handout or an attention control healthy lifestyle handout.

Main Outcomes and Measures: Primary outcomes (assessed at 6 months) are diabetes medication deprescribing (an aggregate measure) and any patient-reported severe hypoglycemia episodes.

Protocol Details

1. **RCT Eligible Participants**–
    a. Kaiser Permanente members aged 75+ years with Diabetes Type 2
    b. Inclusions:
        i. Hemoglobin A1c<=8% (in-control)
        ii. Current use (in prior six months) of insulin and/or sulfonylurea
        iii. Consent to participate in the study
    c. Exclusions:
        i. Deceased
        ii. End of KP Membership
        iii. Does not speak English
        iv. Medical exclusions (Type 1 diabetes, cognitively impaired, palliative care, chemo regime)

2. **Study period**
    a. Patients provisionally enrolled from October 1, 2020-July 31, 2023
        i. Patients provisionally enrolled based on verbal consent
        ii. Enrollment and official consent are upon initial patient encounter with their PCP
    b. Follow-up from October 1, 2020-September 15, 2024
    c. Index Date (T0)
        i. Initial Patient Encounter with their PCP (e.g., visit, secure message) following receipt of packet
    d. Follow-up Period – Analyze two time points
        i. 6 months following the index date (T6)
            1. Follow-up survey may be more than six months after the initial visit, depending on when the RAs are able to successfully contact the patient for the follow-up survey
        ii. 12 months following the index date (T12)

3. **Study Arms**
    a. Study Arm Assignment
        i. PCPs were randomized upon Academic Detailing session attendance
        ii. Patients were assigned to a study arm based on their PCP on file upon enrollment
    b. Arm 1 (Control): Academic Detailing + General Packet
    c. Arm 2 (Intervention): Academic Detailing + Patient Pre-Visit Preparation Packet

Statistical Analysis Plan (SAP)

We will construct generalized estimating equation (GEE) models to compare changes from baseline in clinical and patient-reported outcomes ($p < 0.05$) between clinical trial arms. All statistical analyses will use SAS 9.4 (SAS Institute Inc), and regression models were fit using PROC GENMOD. For each deprescribing, patient-reported and hypoglycemia-related outcome, we will construct a regression model with baseline measurements of the outcome included as covariates and a repeated statement to account for patient clustering within PCP panels. We will also examined heterogeneity of treatment effect (HTE) based on demographic and baseline clinical variables by calculating interaction term p-values from the models with and without interaction terms at 6 and 12 months for the deprescribing primary outcome.

The Table lists each baseline covariate that will be used in each outcome model.

Outcome Model	**Baseline Covariate(s) Included**
Any deprescribing (T6 and T12 models)	On insulin at T0 – y/n and on sulf at T0 – y/n
Self-reported severe hypoglycemia event from T6 patient survey	Self-reported severe hypoglycemia event from T0 patient survey
Hypoglycemia-related ED or IP diagnosis (T6 and T12 models)	Hypoglycemia-related ED or IP diagnosis in 1 year prior to T0
HbA1c lab result (T6 and T12 models)	Latest HbA1c lab result prior to T0 >8%

4. **Outcomes**

Outcome	Timepoints	Summary Statistic in Each Arm and At Each Timepoint	Effect Estimate, Difference in:	Initial Statistical Test
HbA1c Value	Baseline, Follow-up	Mean and CI	Means	T-test
HbA1c <=8	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
Hypo IP	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
Hypo ED	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
ED	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
IP	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
PCP Visits	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
Survey Responses	Baseline, Follow-up	% of Arm	Proportions	Chi-sq
PEPPI Scores	Baseline, Follow-up	Mean and CI	Means	T-test
PAID5 Scores	Baseline, Follow-up	Mean and CI	Means	T-test
RAND PSQ	Follow-up	% of Arm	Proportions	Chi-sq

a. Primary Outcomes
    i. Deprescribing of either insulin or SU
        1. Discontinuation of either insulin or SU
        2. Reduction in dose of insulin or SU
        3. Switch from a higher risk to lower risk version of insulin
    ii. Timeframe for determining baseline and follow-up medication regimen
        1. Single-date regimen at T0, T6, and T12

b. Secondary Outcomes
    i. Changes in HbA1c levels
        1. Baseline HbA1c: Use most recent prior to T0 in the year prior to T0; if no HbA1c in year prior to T0, pull forward eligibility HbA1c
        2. Follow-up T6: in this timeframe, pick the HbA1c closest to T6
        3. Follow-up T12: in this timeframe, pick the HbA1c closest to T12?
    ii. Hypoglycemic-related hospitalizations
    iii. Hypoglycemic-related ED visits
        1. Number of hypoglycemic-related ED visits between T0-T6

c. Patient-reported outcomes (Change between baseline and follow-up questionnaires)
    i. Incidence of patient-reported moderate and severe hypoglycemic events
    ii. Less diabetes-related stress
    iii. Perceived quality of care

5. **Baseline data**
    a. PCP Data
    b. Patient Data
        i. Demographics: Race, Ethnicity, Age, Gender, Language
        ii. Patient Engagement: Kp.org status, Kp.org usage
        iii. Comorbidities Data lookback: 1 year before study visit date
        iv. Clinical Characteristics
            1. Medications: Diabetes Medication Regime (Insulin, Sulfonylurea), Medication Count (All Medications)
            2. Labs: HbA1c
                a. Data lookback: 1 year before study visit date
                b. HbA1c Selection: most recent one prior to T0
            3. Hypoglycemic-related hospitalizations
            4. Hypoglycemic-related ED Visits
        v. Membership/Insurance
        vi. Baseline Survey Responses

6. **Lost to Follow-up**
    a. Reasons
        i. Loss of membership during study period
        ii. Death
        iii. PCP Switches

7. **Analyses**
    a. Comparison of baseline characteristics between intervention and control
    b. Comparison of consented vs declined
        i. Characteristics as of Eligibility Date:
            1. Demographics: gender, age, race, ethnicity, language
            2. Study eligibility data: HbA1c, INS/SU Y/N
    c. Flow through the study
        i. Time from provisional enrollment to actual enrollment
        ii. Reasons for drop out and missing data
    d. Comparison of outcomes between intervention and control
        i. Analysis of subsets of patients based on specific characteristics

8. **Final Analytic Tables**
    a. Enrolled vs Declined
    b. Table 1-Intervention vs Control
    c. PCP Table
    d. Outcomes table

9. **Sensitivity Analysis**
    a. Sensitivity analyses to assess the impact of missing data
    b. Sensitivity analyses based on modality of visit (virtual vs. in-person)
    c. Strata of people who had prior hypoglycemic events