Comparative Effectiveness of Dual Therapeutic Regimens for Diabetes: A BICEP Pragmatic Clinical Trial

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Background

The primary aim of Building Infrastructure for Comparative Effectiveness Protocols (BICEP) was to build an analytical informatics infrastructure for conducting comparative effectiveness research on complex patients in the Connecticut Center for Primary Care Practice-based Research Network. The project goals were to:

- **Assemble electronic clinical information sources** into a single analytic database that links information from all sources by unique patient identifier and standardizes the meaning, coding, and location of data elements from all of these sources.
- **Conduct a pilot study** to demonstrate the feasibility and value of using the analytic database for conducting Comparative Effectiveness Research among complex patients with diabetes and multiple morbidities.

Pilot Study Questions

What is the comparative effectiveness of second-line dual therapy options in decreasing hemoglobin A1c among adults age 20 or older with Type 2 Diabetes Mellitus (T2DM) not achieving glycemic control with mono therapy?

Additionally, what are the factors that mediate the relationship between treatment regimen and change in A1c, and can we control for these factors by testing key covariates in linear regression models?

Innovative Methods

- Assembly of multiple ambulatory care data sources
- Triangulation of disease "concepts" from multiple data sources
- Exclusion of Personal Health Information (PHI) while maintaining data utility
- Adjustment for Multiple Chronic Conditions (MCC)
- Handling of missing data
- Propensity score adjustment non-randomization of treatment
- Time-interdependent Medical Intervention Clusters (MIC)
- Poly characteristics, Poly interventions, Poly outcomes

Methods

700,000+ Potential patient history assessed for eligibility

Exclusion:
- > 352,500 patients not seen 2009-2011
- 87,963 children age 0-17
- 35,413 non-diabetic patients
- 828 patients with Type 1 Diabetes
- 20 patients with "polycystic" disease
- 686 patients with gestational diabetes

Inclusion - Definition of Type 2 Diabetes:
- 20,375 patients with diabetes in Electronic Health Record (EHR) problem list
- 381 patients with A1C > 6.5 at least twice
- Patients with two or more of the following :
  - + Diabetes medication in medication list
  - + Any of 30 specific diabetes medications in text notes
  - + Abnormal glucose test (> 200 mg/dL)
  - + Billing claim diagnosis of diabetes
  - + Diabetes listed in text notes
  - + EHR form name of "diabetes" excl. "pre-diabetes" form

Exclusion: 2,190 patients with <2 visits after baseline

19,571 type 2 diabetes patients

Select data sources and merge with diabetes patients:
- 19,571 Practice Management Demographic Records
- 568,405 Encounter Claims (CPT 992xx-99499)
- 406,396 EHR Office Measures (HT, WT, BMI, BP,…)
- 1,139,144 EHR "Problems" records
- 1,061,546 EHR "Medication" records
- 982,838 Health Maintenance (selected Labs) records

Calculate derived variables
- "Triangulation" for "concepts": i.e. tobacco use

Type 2 Diabetes Dataset

Exclusion:
- 4,099 pts. not on diabetes meds at baseline
- 5,806 pts. on mono-therapy (not insulin)
- 5,626 pts. on >2 oral meds or insulin

Study Cohort: 4,040 type 2 diabetes patients on dual therapeutic regimens defined as:

- **Met-SU** = 1,901 Metformin plus Sulfonylureas
- **Met-TZD** = 881 Metformin plus Thiazolamides
- **Met-DPP4** = 871 Metformin plus Dipeptidyl Peptidase-4
- **Non-Met** = 387 Sulfonylureas plus either DPP4 or TZD

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Results

Model-Based Least Squares Estimated Mean (SE) Change in A1c

Adjustment Factors	Met-SU	Met-TZD	Met-DPP4	Non-Met	p-value[1]
Unadjusted model	-0.13 (0.03)	-0.08 (0.041)	-0.27 (0.04)*	-0.01 (0.06)	<0.001
Adjusted for propensity score (PS)	-0.09 (0.03)	-0.23 (0.04)*	-0.19 (0.04)*	-0.02 (0.06)	0.008
Adjusted for PS, age, and gender	-0.08 (0.03)	-0.22 (0.04)*	-0.18 (0.04)*	-0.01 (0.06)	0.008
Adjusted for PS, age, gender, and:					
Hypertension	-0.15 (0.04)	-0.29 (0.05)*	-0.25 (0.05)	-0.08 (0.07)	0.009
Narcotic analgesics	-0.10 (0.03)	-0.24 (0.04)*	-0.20 (0.04)*	-0.03 (0.06)	0.007
Microalbumin >30 mg/L	-0.06 (0.03)	-0.19 (0.05)*	-0.16 (0.05)*	0.01 (0.07)	0.007
Steroids	-0.09 (0.03)	-0.23 (0.04)*	-0.19 (0.04)	-0.02 (0.06)	0.008
ALT > 56	-0.06 (0.04)	-0.19 (0.05)*	-0.15 (0.05)*	0.02 (0.07)	0.008
Hemoglobin A1c percent	-0.09 (0.03)	-0.22 (0.04)*	-0.19 (0.04)*	-0.03 (0.06)	0.005
Count of HCC	-0.08 (0.03)	-0.22 (0.04)*	-0.18 (0.04)	-0.01 (0.06)	0.008
Anemia	-0.10 (0.04)	-0.24 (0.05)*	-0.20 (0.05)*	-0.03 (0.07)	0.008
Lipid levels	-0.11 (0.03)	-0.24 (0.04)*	-0.21 (0.05)*	-0.04 (0.06)	0.008
Visits post baseline	-0.08 (0.03)	-0.22 (0.04)*	-0.18 (0.04)	-0.02 (0.06)	0.010

- P-value <0.05 comparing mean A1c change to subjects receiving Met-SU dual therapy

[1] Overall p-value for test of equal mean change in A1c by treatment regimen.

Conclusions

The change in A1C differed significantly among dual therapy treatment groups. Differences in A1C persisted with adjustment for a number of covariates. Pragmatic trials on complex ambulatory patients are feasible.

Further possible lines of inquiry include:
- Comparative effectiveness of second-line therapy options in controlling BMI or other indicators
- Comparative occurrence of selected clinical outcomes or adverse events
- Factors affecting the comparative effectiveness of second-line dual therapy options.